Toxicity of local anesthetics

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Systemic neurotoxicity due to excessive cerebral local anesthetic blood levels is one of the most severe and most frequent adverse outcome of local anesthetic use. Toxic levels are most often produced by unintentional intravenous or intraarterial injection(1,2). Toxicity can also result from the rapid absorption of drug following perineural injection. Peak blood levels are usually obtained according to the injection site after 20-40 min. The neurotoxic symptoms are seen in roughly the same progression and proportion with all local anesthetics. The first symptoms are numbness of tongue and lightheadedness followed by visual disturbance, muscular twitching, unconsciousness and ending in convulsions and coma(3,4). The physiopathology is explained by a imbalance between inhibitory and excitatory pathways within the central nervous system. The GABA system-inhibitory – is blocked by high local anesthetic brain levels. The local anesthetics themselves do not produce direct permanent damage to the central nervous system. The depression reverses rapidly as the blood levels fall below the seizure threshold. The major risk to the patient is from cerebral hypoxia during the period of seizures and coma. Hypoxemia is rapid in onset because of the severe muscle activity in conjunction with apnea. Treatment logically consists of oxygenation and support until the blood levels are lowered by redistribution of the drug. Midazolam and propofol are the most useful drugs to treat convulsions induced by local anesthetics(5,6). Both are GABA-agonists and are therefore able to restore a balance between inhibitory and excitatory pathways(7,8). However, propofol may be preferred because of its more favorable pharmacokinetic/pharmacodynamic profile. Several factors influence the actual seizure threshold in a given individual. Any factor that interferes with normal plasma clearance (such as liver failure for the amino esters) will greatly increase the expected toxicity. Hypercarbia as well as metabolic acidosis also will lower the seizure threshold for all drugs. Fortunately central nervous system hyperexcitability can be managed quickly and easily.

The most serious cardiotoxic effects have been reported after accidental i.v. injection or overdose of bupivacaine, and resuscitation of cardiac arrest in such patients can be unexpectedly difficult(9,10). Short-acting LAs are less toxic and almost never involved in serious cardiac complications.

Bupivacaine has a high affinity for cardiac sodium channels and rapidly blocks these during systole, while it slowly dissociates during diastole(11). Bupivacaine also interferes with calcium channels and depresses mitochondrial ATP synthesis(12,13).
Why some patients are more sensitive than others is unclear, but it may depend on a sub-clinical dysfunction of the myocardial sodium channels(14).

Animal studies show that the newer and longacting LA ropivacaine is less arrhythmogenic and cardiodepressive than bupivacaine and levobupivacaine(15,16), and resuscitation of overdosed dogs was more successful after ropivacaine than after bupivacaine or levobupivacaine(17,18).

The patho-physiology of bupivacaine cardiotoxicity indicates that drugs which increase heart rate may contribute to accumulation of bupivacaine in the myocardium, and this may be one reason behind the described difficult resuscitation. Therefore, drugs that improve cardiac performance with little increase in heart rate (eg. nor-epinephrine) may be more effective than drugs with high increase in heart rate(19,20). Amrinone (Inocor®), a phospho-diesterase inhibitor, which restores myocardial ATP, could be useful in these situations(19-22) but clinical experience is limited. Another possibility is amiodarone (Cordarone®), a class III anti-arrhythmicum, which currently is a primary drug in the ACLS antiarhythmia treatment algorithm in the USA. However, its use is not without practical and theoretical problems, and again, clinical experience is limited(23).

An alternative for treating ventricular arrhythmias is bretylium (Bretylol®), a quaternary ammonium compound that prolongs action potentials in the heart and interferes with reuptake of norepinephrine by sympathetic neurons, but again, clinical experience is limited(21).

References


