

# Current Concepts in Resuscitation of Patients With Local Anesthetic Cardiac Toxicity

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**S**evere local anesthetic-induced cardiac toxicity during regional anesthesia is not common.<sup>1,2</sup> Yet the prospect of such an event is daunting,<sup>3,4</sup> thereby warranting interest in its prevention and treatment.

Experimental studies of local anesthetics other than cocaine identify the 2 most important components of local anesthetic cardiac toxicity as arrhythmia and contractile depression.<sup>5-8</sup> Cocaine overdose,<sup>9,10</sup> which also manifests systemic and coronary vasoconstriction<sup>9</sup> and myocardial ischemia or infarction,<sup>11-13</sup> is not addressed in this review. Arrhythmias after local anesthetic overdose include conduction delay, ranging from bundle branch block and prolonged PR interval to complete heart block, sinus arrest, or asystole.<sup>14</sup> Ventricular ectopy is common and may progress to more malignant arrhythmias such as ventricular tachycardia, torsades de pointes,<sup>15</sup> and ventricular fibrillation.<sup>8</sup> Local anesthetics can also depress myocardial contractility,<sup>16</sup> thereby lowering cardiac output and further reducing the likelihood of successful resuscitation from overdose. In the extreme, all these effects can be resistant to treatment. Furthermore, local anesthetic overdose is likely to cause seizures, hypoxia,<sup>17</sup> or acidosis,<sup>18,19</sup> all of which may exacerbate cardiotoxicity. The resulting cycle of systemic and myocardial hypoperfusion, tissue acidosis, and worsening cardiac performance can lead to failed resuscitation.

Severe local anesthetic toxicity is mechanistically complex. A comprehensive review of the chemistry and molecular actions of local anesthetics is beyond the scope of this article.<sup>20-26</sup> Nevertheless, a simplis-

tic explanation of their potential for causing harm is that virtually all local anesthetics are amphiphilic molecules. By having both lipophilic and hydrophilic properties, they can enter a variety of cell compartments and potentially interact with many different cell membranes, organelles, and a host of membrane-bound and cytosolic, charged molecules. When delivered to sensitive tissues (eg, heart, brain, or skeletal muscle) at therapeutic concentrations, they can interfere with cellular metabolism and homeostasis, particularly cell signalling systems and energy transduction pathways. Documented sites of toxic action include ionotropic signaling pathways (sodium,<sup>27,28</sup> potassium,<sup>29,30</sup> and calcium<sup>31</sup> ion channels) and metabotropic pathways such as beta-adrenergic<sup>32</sup> and lysophosphatidate<sup>33</sup> signaling systems that confer information by second messengers rather than by changes in ion flux. Local anesthetics also interfere with G-protein modulation of Ca and K channels,<sup>34,35</sup> cardiac bioenergetics,<sup>36</sup> and mitochondrial dynamics.<sup>37</sup> Local anesthetics also impede adenosine triphosphate (ATP) synthase,<sup>38</sup> the enzyme which converts adenosine diphosphate (ADP) to ATP at the mitochondrial inner membrane.

The apparent ability to affect so many different cellular processes may account for the clinical complexity and potential severity of local anesthetic toxicity.<sup>39-41</sup>

## Preventing Local Anesthetic Overdose

**Preparation.** Prevention begins with making certain that the work environment is optimized for treating an emergency, including tools for airway management and responding to cardiac arrest. Thoughtful selection of the local anesthetic, its dose and concentration, and block technique is also key to safe practice. Optimal concentration is the lowest that achieves the desired effect. Skillful needle tip placement and knowledge of the relevant anatomy also improve safety.

**Pretreatment.** In animals, pretreatment with a benzodiazepine lowers the probability of seizure and death secondary to local anesthetic overdose.<sup>42-48</sup> Although a sedated patient is theoretically less able to inform the physician of a toxicity pro-

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drome, experimental evidence strongly supports benzodiazepine pretreatment. The same is not true of opiate treatment, which can retard the tachycardic response to a test dose.

**Test Dose.** It is desirable to identify intravascular injection as early as possible, thereby lowering the probability of local anesthetic systemic toxicity. Considerable clinical research was conducted in the last decade to determine the best test for detecting intravenous injection, including dye (detected by a change in pulse oximetry),<sup>49</sup> epinephrine (5-15  $\mu$ g), or isoproterenol (3  $\mu$ g).<sup>50</sup> Endpoints considered in establishing sensitivity and specificity to epinephrine include increase in heart rate or systolic blood pressure<sup>51</sup> and a decrease in T-wave amplitude. Test doses are affected by age,<sup>50,52</sup> pregnancy,<sup>53</sup> and superimposed drugs such as clonidine,<sup>54</sup> benzodiazepines,<sup>55</sup> beta blockers, opiates,<sup>55</sup> and general anesthetics.<sup>56,57</sup> After single injection of 15  $\mu$ g epinephrine, acceptable sensitivity is defined in most patients by heart rate increase >10 bpm, increase in systolic BP >15 mm Hg, or 25% decrease in lead II T-wave amplitude.<sup>58</sup> Several studies suggest that blood pressure change is more sensitive for indicating intravascular injection of epinephrine than is heart rate change,<sup>51,56</sup> particularly for patients receiving opiates.<sup>55</sup> Similarly, elderly patients are less responsive to beta stimulation,<sup>59</sup> as are those taking beta-blocking drugs. In these patients, the clinician should be more focused on detecting changes in blood pressure and T-wave morphology after the test dose. The typical delay to increased heart rate after injection is 40 seconds with the maximum increase at 50 to 60 seconds (maximum increase in blood pressure is 90 seconds). Low cardiac output may prolong circulation of the drug.

**Divided Doses.** Slow, incremental injection of local anesthetic, with frequent aspiration and monitoring of the heart rate, will reduce the risk of delivering a toxic dose. Large intravascular local anesthetic doses are better tolerated when injected slowly because longer intervals between injections reduce the possibility of summing intravascular injections. Assuming that a test dose will generally raise the heart rate within 40 seconds, dosing intervals should be on that order or longer. I recommend injecting each increment of 5 mL over 10 seconds or more, then waiting 30 to 40 seconds before the next injection, continually monitoring for changes in heart rate, blood pressure, and T-waves.<sup>50,55,58</sup> Immediately stop injecting if signs of local anesthetic toxicity are detected. Direct intravascular injection is apparent within a minute or less; however, absorption leading to systemic toxicity can be delayed, thus necessitating continual monitoring after injection.

It is logical to reduce local anesthetic dosage in elderly or debilitated patients and in patients with low cardiac output, although there are no specific data to support this recommendation or to specify the degree of dose correction.

## Early Response

Immediate intervention at the earliest sign of toxicity will improve chances of successful treatment.<sup>60</sup> Typical symptoms of early toxicity include auditory changes, visual disturbance (difficulty focusing or diplopia), lightheadedness, apprehension, numbness of the tongue and lips, and drowsiness.<sup>61,62</sup> At higher doses, restlessness, agitation, myoclonus, nystagmus, and slurred speech occur.<sup>63,64</sup> Tachycardia and hypertension can occur after injection of local anesthetic without epinephrine,<sup>65</sup> even concurrent with echocardiographically documented reduction in contractility. Thus, when bradycardia and hypotension occur in the setting of local anesthetic injection they may be indicative of severe overdose.

Once a toxic reaction is recognized, management requires immediate supportive care, instituting Advanced Cardiac Life Support (ACLS), and providing treatment specific for local anesthetic toxicity.

Treatment is aimed at correcting contractile depression and arrhythmia. Groban et al<sup>6</sup> described hemodynamic changes in dogs during local anesthetic overdose and resuscitation. Hypotension was the main cause of cardiac collapse in all local anesthetics examined. Lidocaine required much higher plasma concentrations to achieve this endpoint than did ropivacaine, levobupivacaine, or bupivacaine and required epinephrine for longer periods to support blood pressure. Half of the animals given bupivacaine to the endpoints of cardiovascular collapse did not survive resuscitation, whereas all dogs receiving lidocaine did. Thus, although lidocaine can induce cardiac depression at extremely high plasma concentrations, Groban et al.<sup>6</sup> showed that the lipophilic local anesthetics, specifically bupivacaine (racemic and levo-) and ropivacaine, are far more likely to produce fatal cardiac toxicity.

Because hypercapnia, hypoxia, and acidosis exacerbate bupivacaine-induced toxicity,<sup>17,66</sup> airway management and suppression of seizure activity are key therapeutic interventions. Ventilation is not intended to produce hypocapnea but to aid in normalizing arterial pH and optimizing tissue oxygenation.

Prevention or early treatment of seizure activity is particularly important because seizures produce metabolic acidosis and thereby exacerbate toxicity. Chest compression, cardioversion, or defibrillation

should be provided as needed. Another intervention that must be considered early in bupivacaine toxicity is cardiopulmonary bypass.<sup>67</sup> It is reasonable to think of and plan for this contingency very early in the resuscitation.

### Therapy for Local Anesthetic Toxicity

**Low Output State.** The preponderance of animal studies has shown that resuscitation using sympathomimetics, particularly norepinephrine and epinephrine,<sup>68</sup> improves outcome. This is consistent with the observation that contractile depression is a core feature of severe cardiotoxicity. Furthermore, it is logical to raise blood pressure to support coronary perfusion pressure during resuscitation and facilitate local anesthetic washout. However, sympathomimetic drugs can have adverse effects. Epinephrine can exacerbate arrhythmias associated with local anesthetic overdose<sup>6,68,69</sup> without improving cardiac output.<sup>70</sup> Ventricular fibrillation can be refractory to therapy in the setting of bupivacaine toxicity. Thus, it is worthwhile to consider other vasopressors such as vasopressin in the setting of local anesthetic-induced hypotension.

The use of phosphodiesterase inhibitors for cardiac failure in local anesthetic overdose remains controversial. These drugs are positive inotropes and vasodilators, a combination expected to improve cardiac output, but not necessarily support blood pressure.<sup>71</sup> They are associated with a significant incidence of ventricular arrhythmias.<sup>72</sup> Animal studies of amrinone and milrinone for the treatment of local anesthetic cardiac toxicity have shown conflicting results,<sup>68,73,74</sup> suggesting that phosphodiesterases may improve hemodynamics but not outcome. However, Neustein et al.<sup>70</sup> recently compared milrinone and epinephrine in treatment of ropivacaine-induced cardiac depression in pigs. Milrinone corrected cardiac output, contractility, and blood pressure, whereas epinephrine caused severe hypertension, tachycardia, and ventricular arrhythmias without improving cardiac output.

**Arrhythmias.** Although there is logic in avoiding local anesthetic antiarrhythmics to treat local anesthetic-induced arrhythmias, cardiotoxicity, this issue is far from clear. Amiodarone is now a primary drug in the ACLS arrhythmia treatment algorithm; however, its use is not without practical and theoretical problems. Onset of amiodarone's desired clinical effect is prolonged, and it can produce significant hypotension. Furthermore, amiodarone is a potent inhibitor of ion channels that are mechanistically implicated in bupivacaine toxicity. Haasio et al.<sup>75</sup> used amiodarone in a pig model of bupiva-

caine-induced arrhythmias in the setting of hypoxia and hypercarbia. Survival was 90% in amiodarone treated animals and 60% in those receiving 5% dextrose solution. The differences did not reach statistical significance but may lend support to the use of amiodarone. Although some studies have shown lidocaine to reduce bupivacaine toxicity,<sup>76</sup> others show additive toxicity.<sup>77,78</sup> I believe that on balance the current data support using amiodarone in treating severe bupivacaine-induced arrhythmias.<sup>75</sup>

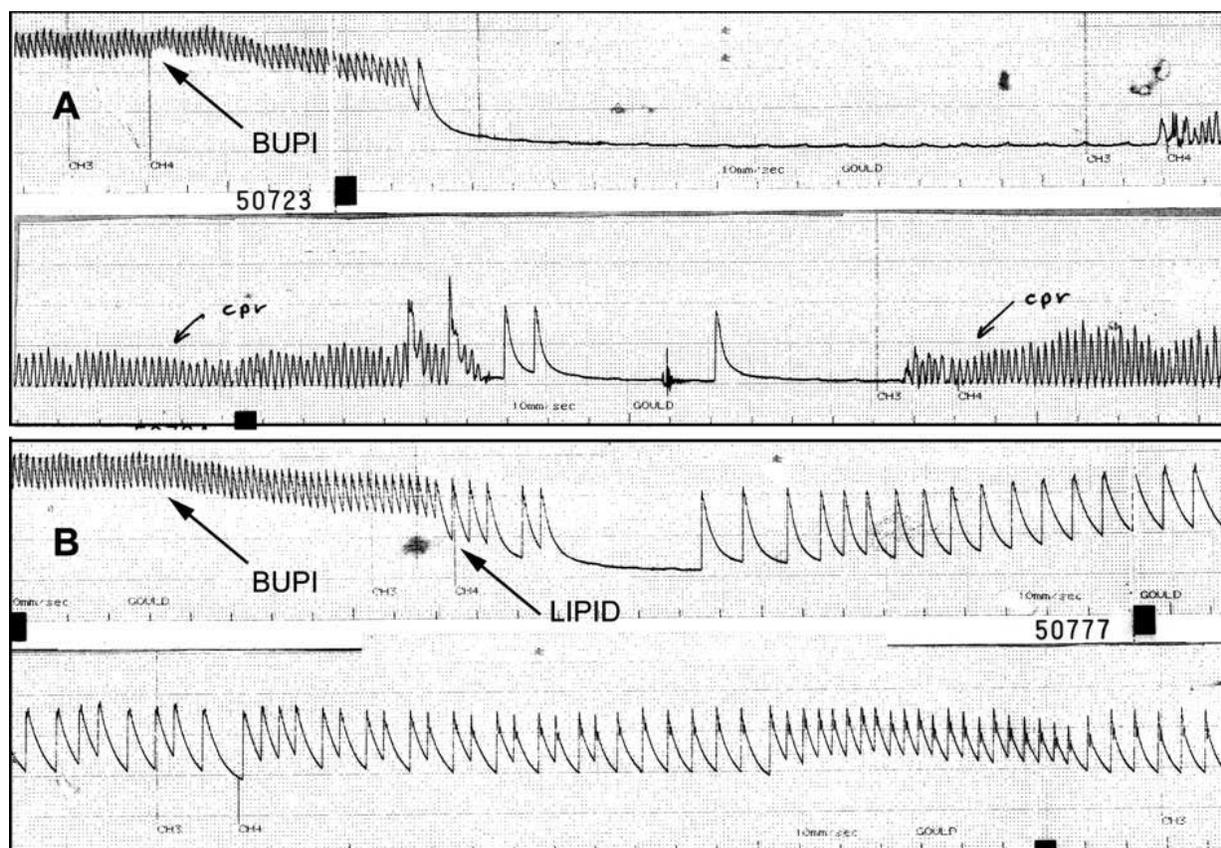
**Vasopressor Support.** The ACLS guidelines now recommend using vasopressin (40 U intravenous, once) in place of, or in addition to, epinephrine. This appears logical in the setting of bupivacaine toxicity because epinephrine may exacerbate local anesthetic-induced arrhythmias.<sup>6,68,69</sup> Krismer et al.<sup>79</sup> recently reported that vasopressin was at least as effective as epinephrine in the resuscitation of ventricular fibrillation in pigs, with or without bupivacaine epidural block. However, their model is not directly applicable to ventricular fibrillation after intravascular bupivacaine injection because they administered bupivacaine in the epidural space and fibrillation was electrically induced. Nonetheless, in cardiovascular collapse, vasopressin supported coronary perfusion better than epinephrine in pigs without epidural block and produced less acidosis than in those receiving epinephrine. Vasopressin requires more complete evaluation as an adjunct in treating bupivacaine overdose.

**Contraindications.** Calcium channel blockers should be avoided in the setting of local anesthetic overdose because coadministration in mice significantly increased lethality as compared with local anesthetic alone.<sup>80</sup> Bupivacaine and calcium channel blockers appear to have an additive depressant effect on myocardial contractility, possibly because of effects on intracellular calcium dynamics and sites such as the calcium-sensitive calcium release (ryanodine receptor) channel.<sup>81</sup> Phenytoin also increases anesthetic toxicity.<sup>78</sup> Use of bretyllium is not supported.

### Novel Modes of Therapy

Use of lipid infusion, propofol, or insulin/glucose/K has not been reported in humans for treatment of local anesthetic overdose; therapeutic guidelines and clinical safety or efficacy of these treatments have not yet been defined.

**Lipid Infusion.** We previously reported that bupivacaine severely impairs transport of fatty acid molecules in cardiac mitochondria,<sup>41</sup> where they are the dominant fuel for normal aerobic metabolism.<sup>82</sup> We reasoned that by increasing the flux of



**Fig 1.** Continuous blood pressure traces (each strip ~25 seconds) in experiments comparing lipid emulsion with saline in the resuscitation of bupivacaine (BUPI) overdose in rats. BUPI arrow indicates injection of 15 mg/kg in both A and B. (A) Development of asystole shortly after injection and failure of chest compressions (cpr) to reestablish sustained circulation. (B) LIPID arrow shows injection of lipid emulsion. Blood pressure trace in B shows prevention of asystole and trend to normalization of circulation within 3 minutes.

fatty acids into cardiac cells, we may be able to overcome bupivacaine-induced blockade of fatty acid transport by mass action. Subsequently, we confirmed that pretreatment with 30% soybean oil emulsion increased the dose of intravenous bupivacaine required to produce asystole in rats<sup>83</sup> by 4.8 times as compared with control animals. Furthermore, after a rapid bolus injection of bupivacaine, infusion of lipid during resuscitation improved outcome (return of normal hemodynamic parameters) compared to controls. Survival was determined for a range of bupivacaine bolus doses in control animals (saline plus chest compressions) versus those receiving a lipid emulsion infusion plus chest compressions. Using lipid infusion during resuscitation increased the bupivacaine use corresponding to 50% mortality (LD50) by 50%. The survival curves used to calculate LD50 were different (at 15 mg/kg, survival was 0% in controls versus 100% in treated animals,  $n = 6$  in both groups) (Fig 1).

An alternative explanation for the salutary effect of lipid infusion is that by artificially creating a lipid

phase in blood, one is able to reduce the effective plasma concentration of lipophilic local anesthetic molecules by extracting them into this lipid phase. Indeed, bupivacaine partitioned into a lipid phase versus a plasma aqueous phase at a 12:1 ratio. Groban et al.<sup>6</sup> found that dogs surviving overdose had much lower local anesthetic plasma concentrations 20 minutes after resuscitation as compared with concentrations at cardiovascular collapse. Perhaps the rapid decrease in available bupivacaine activity found after treatment with the lipid emulsion similarly allows successful resuscitation. Although we are still uncertain by which mechanism the lipid is acting, this experimental technique did salvage a high percentage of animals at bupivacaine doses that were otherwise fatal.

**Propofol.** Ohmura et al.<sup>84</sup> reported that pretreating rats with propofol reduced bupivacaine-induced hypotension independent of the lipid-based carrier effects. Heavner et al.<sup>85</sup> showed that propofol effectively suppressed seizure activity in rats after bupivacaine infusion. Momota et al.<sup>86</sup> re-

ported similar findings for rabbits after lidocaine-induced seizures. Because propofol is an effective anticonvulsant and antioxidant,<sup>87-91</sup> this raises the possibility that it may benefit treatment in early bupivacaine overdose by several mechanisms including (1) the salutary effect of propofol itself in reducing bupivacaine cardiac toxicity, (2) suppressing seizures, (3) lipid-based carrier acts by an extraction mechanism to lessen bupivacaine toxicity, and (4) antioxidant properties may improve recovery from tissue hypoxia.<sup>91</sup>

**Insulin/Glucose/K Infusion.** Cho et al.<sup>92</sup> reported that after the infusion of bupivacaine in dogs (to a mixed venous oxygen saturation of 60%), treatment with a combination of glucose and insulin, with or without potassium, sped recovery of blood pressure, cardiac output, and electrocardiogram compared with control animals given only saline or glucose. They postulate that insulin treatment allows K<sup>+</sup> to enter cells and thereby counters bupivacaine inhibition of transient outward K<sup>+</sup> current, thus improving rates of myocardial repolarization. They also propose effects of insulin on calcium homeostasis, sodium channel dynamics, and possibly catecholamine release secondary to hypoglycemia may account for the benefit of this therapy.

I believe an alternative, energy-related mechanism may explain these findings.<sup>93</sup> The heart normally relies on lipid substrate as its dominant (80%) energy source. When bupivacaine infusion impairs utilization of these substrates, an alternative (eg, carbohydrate) fuel can be used to power cardiac ATP synthesis. An infusion of insulin/glucose will presumably increase intracellular flux through the glycolytic pathway and thereby provide increased concentrations of pyruvate, which is an excellent energy source. We postulate that insulin/glucose infusion corrects a bupivacaine-induced metabolic/energy deficiency, thus providing ATP for normalized cardiac performance. Regardless of the responsible mechanism, this technique offers the potential for a simple means of treating a potentially life-threatening emergency. However, glucose infusion can worsen neurologic outcome after cerebral ischemia. Further studies of this technique's clinical applicability are warranted. It is important to assess the efficacy of insulin/glucose infusion in more severe local anesthetic-induced cardiac toxicity, evaluating neurologic as well as hemodynamic outcome.

### Research Considerations and Models

We recognize the potential for discovering a variety of novel treatments of local anesthetic overdose, but how do we assure safety and efficacy?

Most research has favored studying drugs already part of an accepted ACLS protocol (eg, epinephrine, norepinephrine, atropine, amiodarone, and so on). However, new mechanistically based therapies specific to local anesthetic toxicity may add to the efficacy of standard supportive algorithms like those recommended in the ACLS protocols. Significant advances in developing new treatments require the research community to establish standard protocols for evaluating different remedies, based on common criteria for success and safety. What animal or treatment protocols should be used to test and further optimize the most promising drugs? It is difficult to compare the results of different animal model systems using different toxic challenges and endpoints. I believe we should resolve to improve the standards and endpoints of research in this field.

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