Local Anesthetic Systemic Toxicity

A Historical Perspective

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Abstract: The most feared complication associated with the administration of local anesthetics is the profound and potentially lethal effect that these agents can have on cardiac conduction and function. This review traces the evolution of local anesthetic systemic toxicity beginning with the early deaths associated with the introduction of cocaine into clinical practice. The development of bupivacaine is discussed, with particular emphasis on the delayed recognition and acceptance of its inherent cardiotoxicity. Finally, the origins of lipid resuscitation are reviewed with respect to their theoretical foundation, as well as the confluence of events and experimental investigations that delivered this therapy into clinical practice.

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Despite more than a century of use, and substantial achievements in local anesthetic development and modifications in clinical practice, systemic toxicity has remained a significant and potentially lethal problem. This review places this complication in a historical context, with particular emphasis on the development of lipid rescue for bupivacaine cardiotoxicity, and the extension of lipid therapy beyond cardiotoxicity, and beyond the toxicity of local anesthetics.

THE COCAINE YEARS

It would be difficult to overstate the impact that the introduction of cocaine had on clinical practice or the enthusiasm it generated among early practitioners. Unfortunately, reports of systemic toxicity, often lethal, soon "robbed this peerless drug of much favor in the minds of many surgeons."[1] In an article read before the Kings County Medical Society in 1887, Mattison reviewed 50 cases of "cocaine toxaemia," 4 of which were fatal, and within 4 years, he had collected an additional 76 cases.[1] Although the details of these cases were poorly documented, it was clear that seizures or respiratory failure were often the first manifestation. Deleterious cardiac effects were also evident, but described succinctly using phrases such as "cardiac distress," "rapid intermittent pulse," and "intense palpitations and irregular heart action." In 1 case, cocaine's stimulation of the cardiovascular system was so intense that "heart sounds [were] heard two paces from the patient."

Mattison stressed 2 critical determinants of cocaine toxicity that had been previously promoted by Reclus and Dumont: the quantity of drug and the site of injection, noting that cocaine posed greatest risk when administered "under the skin." He also commended and encouraged Reclus' technique of fractioned injection. However, he took exception with Reclus' assertion that impure cocaine was a significant contributor to these adverse events, commenting, "It has a killing power, per se, and the purer the product, the more decided this may be." Mattison drew several other insightful conclusions that remain relevant to this day. He believed that the reported cases of toxicity were only a small subset of a larger pool, that dangerous or deadly results might follow doses usually considered safe, and that cardiac disease or renal impairment might increase risk of toxicity. He also emphasized the need to have resuscitation drugs immediately available (which at the time included hypodermic ether, ammonia, and caffeine).

THE ASCENT OF PROCAINE

The sketchy details of these clinical cases and their inconsistent clinical presentations left in question whether cocaine fatalities resulted primarily from seizures, respiratory failure, direct cardiotoxicity, or some combination of these factors. What was not in question was the need for a less toxic local anesthetic, a view strongly reinforced by cocaine's significant local tissue toxicity. Because cocaine was known to be a benzoic acid ester, developmental strategies focused on this class of chemical compounds. These efforts led to the synthesis of procaine, 1 of 18 related compounds patented by Einhorn and colleagues in 1904.

Although procaine rapidly supplanted cocaine as the most commonly used anesthetic, systemic toxicity remained a significant concern. In response to this concern, the American Medical Association established the Committee for the Study of Toxic Effects of Local Anesthetics, under the leadership of Emil Mayer. Their initial report was published in 1924 and included a review of 43 fatalities associated with the administration of local anesthetic.[2] Of these, 40 were determined by the committee to have resulted from a direct effect of the anesthetic, including 2 that had been previously ascribed by practitioners to "status lymphaticus," a term that had largely supplanted "visitation of God" and was invoked to confer some specificity to an otherwise idiopathic event.

As noted earlier by Mattison, toxicity was most often heralded by seizures or respiratory failure, although there were cases in which cardiac arrest was reported to occur before apnea and unaccompanied by convulsions. Medical errors accounted for several deaths, some of which resulted from unintentional substitution of cocaine for procaine or errors in drug concentration. In some cases, substitution resulted from "verbal orders pronounced indistinctly." Accordingly, the committee recommended that solutions of local anesthetics be uniquely identifiable, with respect to both drug and concentration, and verbal orders should be used cautiously. Despite its infrequent use relative to procaine, cocaine toxicity accounted for most of the reported cases. The committee stopped short of condemning the use of cocaine, focusing instead on limiting concentration, dose, and routes of administration. Although such practices

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never achieved the status of a "National Patient Safety Goal" and there was no mention of loss of accreditation, the committee did caution that a clinician who did not adhere to such recommendations "is treading on dangerous grounds."

The committee noted that "one of the most striking facts shown by a study of reports is that the occurrence of an accident seldom finds the operator ready to apply suitable measures promptly," and that "in the treatment of accidents, the first place must be assigned to artificial respiration, perhaps with cardiac massage." In contrast, they called attention to the lack of evidence supporting the use of any specific adjuvant, and the potential dangers of morphine and high-dose epinephrine. In noting the limited success of resuscitation, the committee emphasized the role of prevention, commenting, "it should be remembered that, with suitable precautions, the operator will seldom have a serious case of poisoning." Finally, they pointed out that ordinary channels of medical publication are inadequate for documenting such complications and that reporting such events is a duty of the physician, and the sole means by which such complications might be reduced.

TOXICITY REKINDLES IN THE MODERN ERA

With the factors contributing to toxicity better defined and widely recognized, and the use of cocaine nearly eliminated, controversy regarding systemic toxicity subsided, only to reemerge a half-century later after the introduction of 2 long-acting, lipid-soluble local anesthetics. The first of these, bupivacaine, was synthesized in 1957 and was incorporated into clinical practice in Scandinavia 6 years later. Initial toxicity studies demonstrated it to have an LD_{50} that was similar to tetracaine, and one-fourth that of mepivacaine, roughly proportional to their potency as local anesthetics.[3] Etidocaine did not appear until 1970, and it achieved only limited popularity because of its propensity to produce a "reverse differential block," ie, a more profound inhibition of motor than sensory function.

The first serious adverse events were reported shortly after bupivacaine was used in clinical practice and were associated with its use for paracervical block in obstetrics. This technique, although effective for pain relief during labor, had been severely limited by the short duration of analgesia achievable with the available local anesthetics, which set the stage for bupivacaine's rapid acceptance. Tragically, case reports of postblock bradycardia and fetal demise soon followed. In 1969, Beck and Martin[4] reviewed 19,907 cases in which patients received 20 mL of 0.5% bupivacaine for paracervical block and reported 23 cases of fetal death. It is important to note, however, that the issue of fetal bradycardia/demise associated with paracervical block was not unique, or even initially described, with bupivacaine.[5] And to this day, there remains some uncertainty whether bupivacaine poses greater risk to the fetus than other local anesthetics when used for paracervical block, a technique rarely used for labor pain in modern clinical practice. Nonetheless, the occurrence of these cases raised concern regarding the possible toxicity of this agent.

With the exception of its use for paracervical block, early reported adverse events from bupivacaine were largely confined to central nervous system toxicity as would be expected from this class of compounds, and mild cardiovascular toxicity, principally hypotension and bradycardia, the latter generally occurring in the setting of central neuraxial blockade. In 1970, as part of the initial requirement to gain regulatory approval in the United States, Moore et al[6] used bupivacaine for epidural anesthesia and peripheral nerve block in 30 cases. One patient developed a trigeminal rhythm after administration of a 0.5% solution with 1:200,000 epinephrine through a caudal catheter. In the same year, Lund et al[7] reported a series of 514 bupivacaine anesthetics. Aside from cardiovascular effects that were ascribed to the "physiologic effect of peridural anesthesia," there was 1 cardiac arrest, which occurred during the attempted epidural anesthesia. Resuscitation was successful, and the arrest was attributed to unintentional subarachnoid injection of anesthetic.

The first major cardiac complication associated with the use of bupivacaine for peripheral block was reported 8 years later by Edde and Deutsch.[8] Immediately after injection of 20 mL of 0.5% bupivacaine for interscalene anesthesia, the patient developed ventricular fibrillation, from which he was successfully resuscitated. However, similar to previous cases, the authors attributed this arrest to unintentional subarachnoid injection of anesthetic. Whether this was correct or not, the patient's baseline ST-T wave changes, and severe comorbidities, which included a history of congestive heart failure, end-stage renal disease, and profound anemia (hematocrit level, 0.126), might have made it difficult to ascribe the event solely to bupivacaine.

If one were to designate a report that should stand as the sentinel case in the saga of local anesthetic cardiotoxicity, it would be the cardiac arrest of a healthy 31-year-old man after caudal anesthesia reported by Prentiss[9] in 1979. After a negative 5-mL test dose of 1% etidocaine, an additional 20 mL was administered, rapidly resulting in convulsions and, within a minute, ventricular fibrillation. The resuscitation lasted 75 minutes and was impeccable, as evidenced by the near-normal blood gases and the patient's complete recovery within hours of the arrest. Prentiss dismissed hypoxia as a possible factor, noting, "the rapid advent of cardiovascular collapse suggests a direct effect of the etidocaine." He also commented on the remarkable resistance to countershock, which he attributed to the drug's high lipid solubility and extensive protein binding. These insightful conclusions have rarely been adequately acknowledged, being overshadowed by the thoughtful and provocative editorial published by Albright later that year.[10]

Albright's editorial reviewed the cardiac arrests reported by Prentiss and Edde along with 5 other similar cases that had not been previously published. Central to the discussion was that these agents possessed unique cardiotoxicity, and they could induce nearly simultaneous convulsions and cardiac collapse, independent of hypoxia. Albright referenced the work of Steinhaus, who demonstrated that the dose of procaine inducing cardiac depression was 4 times the dose producing respiratory depression, but the difference between these doses for dibucaine, a potent amide anesthetic, was slight. He called attention to the urgent need for experimental studies, including those that might establish the efficacy of available treatment options. As Albright anticipated, the editorial met with harsh criticism worldwide.[11–14] In a series of publications, Moore et al[11] provided evidence for the rapid development of hypoxia and acidosis with anesthetic-induced convulsions and suggested that any delay in reversing this process could account for these cardiac events. In support of this supposition, they referenced their experience with more than 20,000 regional blocks performed with bupivacaine at their institution.[12] There were 32 cases that were complicated by convulsions, and none were associated with cardiac collapse.

EXPERIMENTAL EVIDENCE

The intense debate regarding the exceptional cardiotoxicity of these agents stimulated extensive experimental studies, which

initially produced somewhat conflicting data. Liu et al[15] investigated the cardiotoxicity of several anesthetics, including lidocaine, bupivacaine, and mepivacaine in dogs, and found toxicity proportional to their anesthetic potencies. However, later experiments conducted in the same laboratory reported ventricular fibrillation in 25% of animals given a convulsant dose of bupivacaine, although arrhythmias did not occur in lidocaine-treated animals.[16] Similarly, in an earlier study performed on ventilated cats, de Jong et al[17] found that bupivacaine and etidocaine could induce arrhythmias with doses as low as 60% of those producing convulsions. This did not occur with lidocaine, and the margin between cerebral and cardiac toxicity of lidocaine was reported to be at least 2.5 times wider than with bupivacaine or etidocaine. Studies performed on sheep provided additional support for a lower cardiotoxic threshold of bupivacaine and etidocaine and confirmed that toxicity can be enhanced by hypoxia, hypercarbia, acidosis, and perhaps pregnancy.[18–20] The mechanism of this selective toxicity has proven to be complex but seems to rest, at least in part, by the manner in which these anesthetics bind to the voltage-gated sodium channel. Simply put, lidocaine might be considered a "fast-in and fast-out" local anesthetic, whereas bupivacaine seems to bind in a "fast-in and slow-out" fashion.[21] Experimental interest in this field has continued to the present day and has led to the development of single-enantiomer local anesthetics. The enormity of these data precludes consideration in the present discussion and is the subject of a separate review.[22]

REGULATORY INTERVENTION

In the interim, cases of bupivacaine-induced cardiac collapse continued to occur. By early 1983, the US Food and Drug Administration had received reports from the pharmaceutical industry of 12 well-documented cases of cardiac arrest associated with the use of this anesthetic in obstetrics, 10 of which were fatal, and most associated with the use of the 0.75% solution.[23] Despite appropriate management, resuscitation in these cases was deemed difficult or impossible. The US Food and Drug Administration had also received reports of 8 other cases, 6 fatal, which had been collected by Albright, as well as other cases in which fatalities or severe adverse reactions occurred, but for which the information was inadequate to draw reasonable conclusions regarding causality. In response, the 3 manufacturers of bupivacaine modified their package labeling and issued a "Dear Doctor" letter in September of that year stating that the 0.75% solution of bupivacaine was no longer indicated for obstetrical anesthesia. They further advised against the use of any concentration of bupivacaine for paracervical block (a use which had been specifically not recommended in the labeling). Similarly, because of reports of cardiac arrest and death associated with the use of bupivacaine for intravenous regional anesthesia, and lack of information regarding safe dosages and technique of administration, the letter advised against the use of bupivacaine for this indication. These communications also stressed the importance of an adequate test dose and injection of anesthetic in incremental doses.

Some were quick to point out that it is dose, not concentration, that is the key determinant of toxicity[24] and that fatal cases of cardiac arrest had been associated with bupivacaine administered at concentrations as low as 0.25%, again emphasizing the critical importance of the test dose and fractionated injection. Although these modifications in practice and the proscription against the higher concentration of bupivacaine were certainly effective, they did not completely eliminate risk, and with the exception of cardiopulmonary bypass, treatment options for cardiac arrest remained fairly ineffective.

LIPID RESCUE

The theoretical and experimental underpinnings for lipid rescue existed for several decades before the current confluence of events delivered it into clinical practice. In 1962, Russell and Westfall[25] demonstrated that the duration of anesthesia induced by 20 mg/kg of thiopental in male rats could be shortened by the intravenous administration of commercial solutions of cottonseed or corn oil emulsions.

The potential use of lipid extraction as a toxicological therapeutic intervention was investigated a decade later by Krieglstein et al[26] who studied the effect of a fat emulsion on the fraction of free chlorpromazine in rabbit blood, as well as its influence on chlorpromazine's acute in vivo toxicity. When an emulsion containing soybean oil and soybean phospholipids was added to rabbit blood, it caused a significant decrease in the fraction of free chlorpromazine, consistent with the emulsified fat providing a storage depot. Even more critical, when a large dose of chlorpromazine was administered, all animals pretreated with lipid emulsion survived, whereas this dose of chlorpromazine was uniformly fatal to animals that were untreated or treated with control solutions. These findings led Krieglstein et al to conclude, "From the present results it might be concluded that a fat emulsion in blood can take up lipophilic drugs, reduce their fraction dissolved in plasma water and thus decrease their actual availability at sites of action. Whether this effect may be used for therapeutic management of poisoning due to CPZ [chlorpormazine] or other lipophilic drugs remains to be shown."

Despite these findings and their implications, several decades would pass before the identification and clinical application of lipid resuscitation as a practical and apparently effective antidotal therapy for systemic local anesthetic toxicity. And this would come about entirely independent of these early experimental observations, resulting instead from a series of clinical events, insightful observations, systematic experimentation, and astute clinical decisions. In addition, this recent experience and experimentation have served as the catalyst for applications that go well beyond treating the problem of bupivacaine cardiotoxicity.

Intrigued by a case of apparent cardiotoxicity from only 22 mg of bupivacaine administered subcutaneously to a patient with carnitine deficiency, Weinberg et al[27] postulated that this congenital metabolic derangement led to enhanced toxicity from accumulation of fatty acids within the mitochondria. Subsequent studies seemed to provide support for this theory by demonstrating that bupivacaine inhibits carnitine acylcarnitine translocase, a key element of the carnitine shuttle required for the uptake of fatty acids into the mitochondria.[28] Accordingly, Weinberg et al[29] hypothesized that administration of lipid would *potentiate* cardiotoxicity because of this inhibition of mitochondrial metabolism and the resulting accumulation of cytoplasmic fatty acids. However, the experiments to test this hypothesis found the opposite result: pretreatment or resuscitation with lipid substantially shifted the dose-response curve for bupivacaine cardiotoxicity in rats, promoting survival from lethal doses of anesthetic. Encouraged by this unexpected finding, Weinberg et al[30] instituted a series of investigations, which demonstrated the efficacy of intravenous lipid for treating the notoriously resistant cardiotoxicity of bupivacaine—at least in these animal models. Clinical confirmation lagged behind considerably, occurring 8 years after the initial laboratory studies were published.

Faced with a patient who developed cardiotoxicity refractory to standard advanced cardiac life support after receiving 20 mL

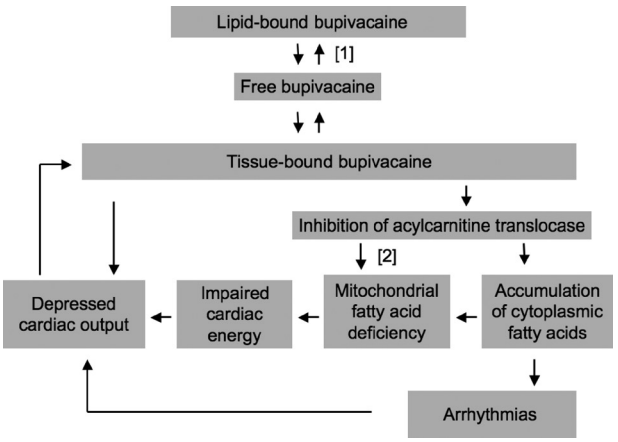

FIGURE 1. Sites of maintenance and potentiation of bupivacaine cardiotoxicity. Lipid intervention might exert a positive effect secondary to 2 postulated mechanisms: [1] lipid sink, with bupivacaine partitioned into lipid, reducing the effective unbound fraction available for binding to cardiac tissue; [2] lipid-providing substrate, which may overcome the loss of cardiac energy due to bupivacaine's inhibition of acylcarnitine translocase.

of 0.5% bupivacaine and 20 mL of 1.5% mepivacaine for an interscalene block, Rosenblatt et al[31] administered a 100-mL intravenous bolus of 20% Intralipid. The patient subsequently responded to defibrillation and ultimately made a complete recovery. A second report by Litz et al[32] extended the potential utility of lipid resuscitation beyond bupivacaine, documenting apparent efficacy for the treatment of cardiotoxicity induced by ropivacaine. Other case reports soon followed,[33–36] providing further support of lipid's clinical utility.

Experimental work and/or anecdotal clinical reports suggest that lipid may have utility for treating local anesthetic central nervous system toxicity,[33,37] as well as toxicity induced by other classes of compounds. Laboratory investigations have demonstrated efficacy for treatment of cardiotoxic challenges from a diverse group of compounds including chlorpromazine,[26] propranolol,[38] chlomipramine,[39] and verapamil,[40] while there are clinical cases of successful resuscitations from bupropion-induced cardiovascular collapse[41] and haloperidol-induced multiform ventricular tachycardia (A.J. Sirianni, MD, personal communication, March 4, 2009).

The mechanism by which lipid may be effective is incompletely understood, but its predominant mechanism is likely related to its ability to extract bupivacaine (or other lipophilic drugs) from aqueous plasma or tissue targets, thus reducing their effective concentration at target sites of action ("lipid sink"). Alternatively, or additively, bupivacaine has been shown to inhibit fatty acid transport at the inner mitochondrial membrane, and lipid might act by overcoming this inhibition, and thus serve to restore energy to the myocardium (Fig. 1). Additional experimental studies and further clinical experience are clearly required to establish the actual mechanism(s) and to identify the optimal parameters of administration, the full spectrum of clinical utility, and any potential adverse effects.

Nearly a century ago, Mayer's committee stressed the importance of having the ability to "apply suitable measures promptly" for resuscitation from systemic anesthetic toxicity. The fact that "suitable" now includes a therapy that might actually be effective represents one of the most important milestones in regional anesthesia, regardless of any lingering uncertainty of its mechanism.

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