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CASE REPORT

PATHOLOGY/BIOLOGY; TOXICOLOGY

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Fatality Involving Complications of Bupivacaine Toxicity and Hypersensitivity Reaction*

ABSTRACT: This case represents unusual findings of elevated bupivacaine and tryptase concentrations following local anesthetic, bupivacaine, administered as a scalene nerve block for elective rotator cuff repair surgery. Following bupivacaine injection, the patient exhibited almost immediate seizure activity, bradycardia, and cardiac arrest. Resuscitative efforts including cardiopulmonary bypass restored a cardiac rhythm. However, the clinical medical status of the patient progressively declined and he died 7 h following administration of the local anesthetic. Autopsy revealed several abnormalities of the heart including cardiomegaly, myocardial bridging, and lipomatous hypertrophy of the intraatrial septum, which may have contributed to bradycardia and arrhythmia. Postmortem toxicology results revealed elevated bupivacaine and tryptase concentrations. Elevated postmortem bupivacaine concentrations 7 h following administration and abrupt onset of seizures indicate unintentional intravascular injection instead of nerve and tissue infiltration. An elevated postmortem tryptase concentration points to the possibility of a hypersensitivity reaction to bupivacaine.

KEYWORDS: forensic science, forensic pathology, bupivacaine toxicity, hypersensitivity reaction, tryptase, forensic toxicology

Bupivacaine (Marcaine®, Sensorcaine®) is an amide local anesthetic that is structurally related to lidocaine and mepivacaine. Bupivacaine stabilizes the neuronal membrane and prevents both the generation and the conduction of nerve impulses, thereby exerting local anesthetic action. Although the pharmacological affects of bupivacaine are rapid and long lasting, the onset and duration of action depends on a number of factors including site of injection, route of administration, and concentration of the anesthetic. Several adverse side effects of bupivacaine have been reported including hypotension, bradycardia, loss of consciousness, confusion, muscular twitching, convulsions, respiratory depression, respiratory arrest, and/or cardiovascular depression (1,2). However, when administered in recommended doses and concentrations, it does not ordinarily produce any toxicity or tissue irritation.

Pharmacokinetic properties of bupivacaine include a peak plasma concentration in 10–20 min following a 400 mg dose of the drug during a bilateral intercostal nerve block, volume of distribution of 0.4–1.0 L/kg, protein binding of 92%, and a half-life of 1.3–2.8 h (1). From the site of injection, bupivacaine slowly enters the systemic circulation and is metabolized in the liver by cytochrome P450 enzymes and excreted by the kidneys as pipecolylxylidine, the major metabolite, and other glucuronide conjugates (1,3).

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Contraindications for bupivacaine use include hypersensitivity reactions to bupivacaine or amide-type local anesthetics and its use as obstetrical paracervical block anesthesia (4). Bupivacaine use is also not recommended for patients less than 12 years old and it should be used with caution in patients with hepatic impairment (4). Relatively small doses of local anesthetics injected into the head and neck area may produce adverse effects similar to systemic toxicity. Importantly, central nervous system (CNS) manifestations of bupivacaine toxicity occur at lower concentrations compared to cardiovascular symptoms (2). Some of these adverse effects are because of an unintentional intravascular injection or systemic toxicity following an overdose (5).

In the present case, the decedent underwent an elective shoulder surgery to repair his injured right rotator cuff. An interscalene brachial plexus block was used as a local anesthetic. The postmortem toxicology, autopsy findings, and pertinent case information are presented.

Case History

A 37-year-old Caucasian male with a history of right rotator cuff injury underwent an elective shoulder surgery. A year prior, the patient had successful surgical repair of his left shoulder with bupivacaine nerve block; therefore, he requested a similar nerve block during surgery of his right rotator cuff. In preparation for surgery, he was injected with bupivacaine near his scalene nerve. Immediately after the injection of the anesthetic, the patient developed bradycardia, seizures, and had a cardiac arrest. He underwent cardiopulmonary resuscitation for approximately 2 h prior to being placed on cardiopulmonary bypass, but died approximately 7 h postinjection of the anesthetic. An autopsy was performed, and postmortem samples were collected for toxicological analysis.

Autopsy revealed several abnormalities of the heart including cardiomegaly, myocardial bridging, and lipomatous hypertrophy of the intraatrial septum, which may have contributed to bradycardia and arrhythmia. Several autopsy findings including rash and laryngeal edema are known to be associated with anaphylaxis, yet these findings have low sensitivity. No signs of anaphylaxis were observed in the decedent at autopsy; however, anaphylaxis cannot be ruled out because of low sensitivity.

Methods

Postmortem cardiac and subclavian blood, vitreous humor, gastric contents, liver, and brain tissue were submitted for toxicological analysis; however, antemortem blood was unavailable for analysis. The analysis included a blood enzyme immunoassay (EIA) screen for nine drugs of abuse, a volatile screen by gas chromatography linked to flame ionization detector (GC-FID), and a drug screen by an alkaline liquid–liquid drug extraction followed by gas chromatography-mass spectrometry. Fluorescent EIA was used for the quantification of tryptase. GC-FID was used for the quantification of propofol. Gas chromatography linked to nitrogen phosphorus detector was used for the quantification of bupivacaine. The postmortem toxicology results are summarized in Table 1.

Results and Discussion

There have been reports of cardiac arrest with difficult resuscitation or death following bupivacaine use despite adequate preparation and appropriate management (6–10). Several studies have determined the plasma concentration at which bupivacaine produces adverse effects and CNS toxicity. Scott et al. determined the bupivacaine concentration and time needed to produce CNS toxicity, by identifying CNS symptoms, is between 1 and 2 μg/mL. The average time to produce these adverse effects is 4 minutes postinjection of the anesthetic (11). In the present case, the cardiac bupivacaine concentration of 1.1 μg/mL falls between the CNS toxic concentration of 1–2 μg/mL reported by Scott et al. (11). Other adverse effects such as tonic-clonic seizures developed 30 sec postremoval of the block needle in one case and were noticed within 3 minutes in another case (7,8). In the presented case, seizure activity was noticed immediately postinjection of the local anesthetic. CNS toxicity has been observed at plasma bupivacaine concentrations between 2 and 4 μg/mL or a mean free plasma concentration of 0.3 μg/mL (2,12). However, two patients who survived had bupivacaine concentrations of 2.37 μg/mL in arterial blood and 3.86 μg/mL in venous blood (12,13). Reports of toxic manifestations of bupivacaine including hypotension, bradycardia, convulsions, and delayed respiratory arrest have been reported at blood concentrations as low as 0.3 μg/mL (1).

Patients receiving local head and neck anesthesia may be at greater risk of CNS and cardiac toxicity because of a greater risk of inadvertent intravascular injection or injection into a highly vascular tissue area. This would result in rapid absorption of the local anesthetic into the systemic circulation causing cardiac sequelae. In the presented case, bupivacaine concentrations were measured in postmortem cardiac and subclavian blood 7 h following administration of the local anesthetic with concentrations of 1.1 and 0.77 μg/mL, respectively. An elevated concentration of bupivacaine in the blood taken 7 h postinjection is indicative of an intravascular injection. Taking into account that the patient was alive for 7 h postinjection and the half-life of bupivacaine is about 2 h, we estimate that the concentration of bupivacaine was most likely much higher at the time of seizure activity than at the time of sample collection because of intraventricular blood stasis resulting from cardiopulmonary bypass. However, it cannot be ruled out that the postmortem cardiac blood analyzed had a similar bupivacaine concentration at the time of seizure activity because of the fact that the decedent underwent cardiopulmonary bypass for 5 h.

Cardiovascular toxicity because of bupivacaine, to some extent, is related to the reduced conduction in the heart by blockade of sodium channels (14), especially in cases of cardiomegaly. It has been reported that bupivacaine is more cardiotoxic than other structurally related local anesthetics, such as lidocaine (14–16). Differences in cardiotoxicity are proposed to be related, in part, to the manner in which the local anesthetics enter and bind to the myocardium. Bupivacaine has the ability to induce a fast in, but slow dissociation block of myocardium sodium channels relative to other local anesthetics (14,16) resulting in a relative decreased rate of membrane depolarization. Therefore, bupivacaine can induce cardiac abnormalities such as torsade de pointes, ventricular tachycardia, multiform premature ventricular contractions, ventricular fibrillation, and refractory asystole at a greater potency than lidocaine or ropivacaine (16). Furthermore, bupivacaine has also been shown to produce peripheral vasodilation and impair heart mitochondrial energy transduction (14,15,17).

TABLE 1—*Postmortem toxicology results.*

Subclavian Blood (EIA)	Result
Amphetamine	Negative
Barbiturates	Negative
Benzodiazepines	Negative
Cannabinoids	Negative
Cocaine metabolite	Negative
Methadone	Negative
Opiates	Negative
Phencyclidine	Negative
Propoxyphene	Negative
Subclavian Blood (GC)	
Bupivacaine	0.77 μg/mL
Cardiac Blood (GC-FID)	
Negative for ethanol, methanol, isopropanol, and acetone	

Subclavian Blood (GC-MS Screen)	
Bupivacaine, propofol, and lidocaine	
Cardiac blood (GC)	
Bupivacaine	1.1 μg/mL
Propofol	91 ng/mL
Postmortem serum (FEIA)	
Total tryptase	45.1 ng/mL (cardiac)
Total tryptase	7.4 ng/mL (subclavian) (Reference range <11.4 ng/mL)

Autopsy findings, in this case, revealed a heart weight of 430 g, a body weight of 240 lbs, and a body height of 69.75 inches (177.2 cm). A healthy normal male has a heart weight of 300–350 g, but may vary with body height and weight (18). Using data obtained by Kitzman et al. (19), an average predicated normal heart weight as a function of body height and weight would be 324 g in a 69.3 inch (176 cm) man or 406 g in a 238 lb man. The increased heart weight indicates repolarization dispersion in this case.

Autopsy also revealed hypertrophic cardiomyopathy (HCM), lipomatous hypertrophy of the interatrial septum (LHIS), and myocardial bridging of the proximal left anterior descending coronary artery. HCM is a common genetic disease of cardiac myocytes characterized by cardiac hypertrophy, an increased or preserved left ventricular ejection fraction, myocyte disarray, myocardial fibrosis, myocardial bridging of epicardial coronary arteries, and anomalies of the mitral valve leaflets (20,21). HCM causes diastolic dysfunction with a reduced stroke volume and can obstruct left ventricular outflow in some patients (18,20). HCM was initially perceived as a rare malignant disease; however, a retrospective study estimated that HCM is relatively common with an estimated prevalence of 1:500 in the general population (22). HCM is the most common genetic myocardial disorder in which myocardial bridging is a frequently encountered coronary arterial anomaly (20).

A myocardial bridge is a congenital anatomical variation defined as an intramyocardial course of a major epicardial coronary artery (23,24). One cohort study showed a 15% prevalence of myocardial bridging in HCM cases and the majority of cases, in general, affected the left anterior descending artery as seen in this case (20,23,24). Myocardial bridging, however, has been found to have no direct association with sudden cardiac death at postmortem in adults with HCM (20). Conversely, it has been proposed that myocardial bridges are a contributing factor in development of angina, myocardial infarction, dysrhythmias, sudden cardiac death, and myocardial ischemia (23,24).

Lipomatous hypertrophy of the interatrial septum is a rare condition characterized as adipose tissue deposits in the interatrial septum that can lead to fatal arrhythmias and sudden death (25,26). Furthermore, LHIS is characterized as a thickness of >2 cm of adipose tissue in the interatrial septum (26). The decedent had a 2.5×1 cm area of interatrial septal lipomatous hypertrophy. The cardiac abnormalities of the decedent along with the cardiotoxic properties of bupivacaine may have contributed to an increased vulnerability to cardiac arrhythmias or may have been incidental findings unrelated to bupivacaine. The effects of bupivacaine are unknown with these cardiac findings.

Lidocaine and propofol were detected in the subclavian blood. Propofol was used to sedate the patient prior to surgery, and lidocaine was administered after the patient went into cardiac arrest. Lidocaine was not quantified in this case, but propofol was quantified at a concentration of 91 ng/mL in postmortem cardiac blood. The role, if any, which the decedent's sedation of propofol infusion played in his death is uncertain. Adverse effects of propofol include bradycardia, hypotension, cardiac arrhythmia, and seizures (1). Therefore, propofol may have potentiated the effects of bupivacaine.

The other contributory factor in the death of the present case may be explained as a hypersensitivity reaction to bupivacaine. A case report detailing a delayed hypersensitivity reaction to bupivacaine can be found in the medical literature (27). Tryptase, a component of mast cell secretory granules, is elevated when mast cell activation occurs and serves as a marker of anaphylaxis. Tryptase is reasonably stable over a period of days and, therefore, can be measured in postmortem samples. It has been used in assisting the forensic pathologist when determining the cause of death from anaphylaxis. In cases of a suspected anaphylactic reaction, laboratory analysis should include tryptase measurements accompanied with analysis of allergen-specific IgE antibodies and/or total IgE. In the presented case, a total IgE was attempted in postmortem blood, but because of matrix interferences, a value could not be determined and the assay of bupivacaine-specific IgE is not available. The laboratory results should be interpreted in the context of the entire case history, and the temptation to rely on a single laboratory assay for the diagnosis of anaphylaxis postmortem should be avoided.

The presented case illustrates a moderately elevated total tryptase concentration of 45.1 ng/mL in postmortem cardiac serum and 7.4 ng/mL in postmortem subclavian serum. The discrepancy between the cardiac and subclavian tryptase concentrations may be due to intraventricular blood stasis resulting from cardiopulmonary bypass, whereas subclavian blood was actively circulating throughout intervention. Furthermore, tryptase peaks within 15–120 min postexposure to the allergen and follows first-order kinetics with a half-life of 1.5–2.5 h (28); therefore, approximately 3 half-lives had elapsed between symptomatic onset and serum collection. Thus, obtained subclavian serum tryptase concentrations are expected to be much lower than values at symptomatic onset if in fact an anaphylactic reaction occurred. The moderately elevated cardiac tryptase concentration in conjunction with the cardiac arrest and rapid onset of seizure activity postinjection of bupivacaine indicates the possibility of an anaphylactic reaction. However, it is possible that this moderate increase in cardiac tryptase is because of lysis of mast cells in the tissue of the chest. At autopsy, there was a large area of subcutaneous hemorrhage of the chest wall because of prolonged cardiopulmonary resuscitation.

Conclusion

Based on the temporal relationship of cardiac arrest and seizure activity following the local anesthetic infusion, autopsy findings of cardiac abnormalities, and toxicology findings of an elevated bupivacaine and tryptase concentration, the cause of death was determined to be complications of the local anesthetic, bupivacaine, for local nerve block for shoulder surgery. The mechanism of death was cardiopulmonary arrest, and manner of death was accident. The moderately elevated cardiac tryptase concentration raises the possibility of anaphylaxis that may have contributed to the cause of death.

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References

1. Baselt RC. Disposition of toxic drugs and chemicals in man, 8th edn. Foster City, CA: Biomedical Publications, 2008;188–90.
2. Knudsen K, Beckman SM, Blomberg S, Sjövall 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.
3. Gantenbein M, Attolini L, Bruguerolle B, Villard PH, Puyoou F, Durand A, et al. Oxidative metabolism of bupivacaine into pipecolylxylidine in humans is mainly catalyzed by CYP3A. Drug Metab Dispos 2000;28: 383–5.
4. Lacy CF, Armstrong LL, Goldman MP, Lance LL. Lexi-Comp's drug information handbook. Hudson, OH: Lexi-Comp, 2004;201–3.
5. Yokoyama M, Ohashi I, Nakatsuka H, Mizobuchi S, Toda Y, Matsumi M, et al. Drug-induced liver disease during continuous epidural block with bupivacaine. Anesthesiology 2001;95(1):259–61.

6. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51(4):285–7.
7. Long WB, Rosenblum S, Grady IP. Successful resuscitation of bupivacaine-induced cardiac arrest using cardiopulmonary bypass. Anesth Analg 1989;69(3):403–6.
8. 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.
9. Marx GF. Bupivacaine cardiotoxicity—concentration or dose? Anesthesiology 1986;65:116.
10. Reiz S, Nath S. Cardiotoxicity of local anesthetic agents. Br J Anaesth 1986;58(7):736–46.
11. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 1989;69(5):563–9.
12. Kreitzer JM, Reuben SS. Central nervous system toxicity in a patient receiving continuous intrapleural bupivacaine. J Clin Anesth 1996;8(8): 666–8.
13. Tuominen MK, Pere P, Rosenberg PH. Unintentional arterial catheterization and bupivacaine toxicity associated with continuous interscalene brachial plexus block. Anesthesiology 1991;75:356–8.
14. de La Coussaye JE, Bassoul B, Albat B, Peray PA, Gagnol JP, Eledjam JJ, et al. Experimental evidence in favor of role of intracellular actions of bupivacaine in myocardial depression. Anesth Analg 1992;74(5):698–702.
15. Yazzie J, Kelly SC, Zumwalt RE, Kerrigan S. Fatal bupivacaine intoxication following unusual erotic practices. J Forensic Sci 2004;49(2): 351–3.
16. Naguib M, Magboul MM, Samarkandi AH, Attia M. Adverse effects and drug interactions associated with local and regional anaesthesia. Drug Saf 1998;18(4):221–50.
17. Sztark F, Malgat M, Dabadie P, Mazat JP. Comparison of the effects of bupivacaine and ropivacaine on heart cell mitochondrial bioenergetics. Anesthesiology 1998;88(5):1340–9.
18. Kumar V, Abbas AK, Fausto N, editors. Robbins and Cotran pathologic basis of disease, 7th edn. Philadelphia, PA: Elsevier Inc., 2005;556–606.
19. Kitzman DW, Scholz DG, Hagen PT, Ilstrup DM, Edwards WD. Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity): a quantitative anatomic study of 765 specimens from subjects 20 to 99 years old. Mayo Clin Proc 1988;63(2):137–46.
20. Olivotto I, Girolami F, Nistri S, Rossi A, Rega L, Garbini F, et al. The many faces of hypertrophic cardiomyopathy: from developmental biology to clinical practice. J Cardiovasc Transl Res 2009;2(4):349–67.
21. Marian AJ. Contemporary treatment of hypertrophic cardiomyopathy. Tex Heart Inst J 2009;36(3):194–204.
22. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002;287(10):1308–20.
23. Loukas M, Curry B, Bowers M, Louis RG Jr, Bartczak A, Kiedrowski M, et al. The relationship of myocardial bridges to coronary artery dominance in the adult human heart. J Anat 2006;209(1):43–50.
24. Denktas AE. Bridge over troubled coronary artery/muscular bridge causing non-ST-segment elevation myocardial infarction. Anadolu Kardiyol Derg 2007;7(1):99–100.
25. O'Connor S, Recavarren R, Nichols LC, Parwani AV. Lipomatous hypertrophy of the interatrial septum: an overview. Arch Pathol Lab Med 2006;130(3):397–9.
26. Heyer CM, Kagel T, Lemburg SP, Bauer TT, Nicolas V. Lipomatous hypertrophy of the interatrial septum: a prospective study of incidence, imaging findings, and clinical symptoms. Chest 2003;124(6):2068–73.
27. Nettis E, Colanardi MC, Calogiuri GF, Foti C, Priore MG, Ferrannini A, et al. Delayed-type hypersensitivity to bupivacaine. Allergy 2007;62(11): 1345–6.
28. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunol Allergy Clin North Am 2006;26:451–63.

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