CARDIOVASCULAR COLLAPSE FROM LOW DOSE BUPIVACAINE

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ABSTRACT

Bupivacaine is a long-acting local anesthetic agent that is very widely used for cutaneous infiltration, peripheral nerve blocks, epidural anesthesia, and spinal anesthesia. Well-described cardiotoxic effects of bupivacaine and other members of its class include dysrhythmias, hypotension, and depression of cardiac output. The minimum IV dose of bupivacaine previously associated with significant toxicity in humans is 1.6 mg/kg. A case is reported of bradyasystolic arrest with post resuscitation shock, without significant central nervous system (CNS) toxicity, following the injection of less than 1.1 mg/kg bupivacaine in an adult.

***Key Words**: bupivacaine, adverse reactions, local anesthetic agents, toxicity, shock, propofol*

Bupivacaine is a commonly used local anesthetic agent with broad applications. Routine uses include local infiltration, regional nerve blocks, epidural anesthesia, and spinal anesthesia. Bupivacaine is a member of the amino-amide subclass of local anesthetics, which was first synthesized in 1963. Bupivacaine is especially popular among the members of its class given its long duration of action and its low incidence of adverse reactions.

Like all local anesthetics, bupivacaine's activity is primarily attributed to reversible blockade of neuronal sodium channels. Sodium channel blockade is also the major mechanism of toxicity in the CNS and cardiovascular system for local anesthetics. Well-described manifestations of systemic toxicity include tinnitus, lightheadedness, circumoral numbness, visual and auditory disturbances, altered mental status, seizures, dysrhythmias, respiratory arrest, hypotension, and shock.

Ordinarily, CNS toxicity of local anesthetic agents occurs at lower serum concentrations than does cardiovascular toxicity; this is especially true of lidocaine and most of the shorter-acting agents. The longer-acting, more lipophilic agents, such as bupivacaine, have been noted to cause cardiovascular toxicity at serum levels that are not much greater than those required to cause CNS toxicity. Previously it was thought that the minimum IV dose of bupivacaine required to produce toxicity in humans was 1.6 mg/kg. A case of cardiovascular collapse following the injection of less than 1.1 mg/kg of bupivacaine in an adult male is reported.

Case Presentation

A 65 year-old, 70 kg male with a history of chronic, multi-level, radicular pain underwent a lumbar sympathetic ganglion radio frequency ablation by the anesthesiology pain service, to control his pain.

A similar procedure one year previously had brought him significant relief. His past medical history also included cervical central cord syndrome, status post cervical fusion, hypertension (not requiring treatment), and a perioperative, non-q-wave myocardial infarction associated with sepsis, two and a half years previously. Echocardiography following the myocardial infarction had demonstrated inferior hypokinesis and a left ventricular ejection fraction (LVEF) of 55%. Coronary angiography at that time demonstrated no coronary disease. The patient had no known drug allergies. His outpatient medications were celecoxib, morphine, amitriptyline, and carbamazepine.

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During the ablation procedure, carried out under propofol infusion, the patient received a 15 mL 0.5% (1.1 mg/kg) plain bupivacaine injection into the left lumbar sympathetic chain shortly following radio frequency ablation of the same. Whether or not aspiration was performed before injection was not documented. Immediately following the bupivacaine injection, a respiratory arrest with bradycardia and hypotension to 54/40 mmHg was observed. Propofol was stopped, ventilation was provided by bag-valve-mask, and the patient was given 25mg ephedrine IV. Spontaneous respirations returned and the patient was transferred to the post-anesthetic care unit (PACU.) Within two minutes of arrival in the PACU, the patient had a sudden asystolic cardiac arrest. The patient was again ventilated by bag-valve-mask and chest compressions were initiated.

The patient was given a total of 2 mg epinephrine IV. Spontaneous circulation was restored after approximately four minutes and the patient regained consciousness. Initial post-resuscitation vital signs were blood pressure 201/129 mmHg and pulse 136 bpm. He was alert and oriented and was without complaints except a headache. No convulsive activity was noted during the arrest. Approximately 30 minutes after the second arrest, the patient became hypotensive to 74/52 mmHg with pulse of 97 bpm. He required a one-liter fluid bolus, and five 100 mcg doses phenylephrine IV to raise his blood pressure to greater than 80 mm Hg systolic. The patient was transferred to the intensive care unit (ICU.)

On arrival in the ICU, the patient's vital signs were blood pressure 73/45 mmHg, heart rate 99 bpm, respiratory rate 19 per minute, and temperature 98.3^{o}F. SpO_2 was 100% on high flow oxygen by non-rebreather mask. The patient was completely alert and oriented and had no complaints. Initial electrocardiogram (ECG) upon arrival in the ICU is shown in figure 1.

When compared to his old ECG, this tracing showed a significant loss of QRS voltage in all leads, a rightward shift in the QRS axis and a new first degree AV block; the QRS and QT intervals were unchanged. Central venous access was obtained via introducer sheath placed in the right internal jugular vein. Dopamine 10 mcg/kg/min IV was given for shock and 50 mg diphenhydramine IV and 125 mg methylprednisolone IV were given IV for a suspected anaphylactoid reaction. Physical examination was only notable for dense rales in all lung fields. Subsequently the patient became dyspneic with decreasing SpO_2 despite high flow supplemental oxygen. Then, he developed a cough productive of pink, frothy sputum. Endotracheal intubation was performed following rapid sequence induction with etomidate and succinyl choline. Artificial ventilation with 100% oxygen raised his SpO_2 above 95%.

Chest radiograph (figure 2) demonstrated patchy interstitial and alveolar infiltrates in all fields, greatest inferiorly. A Swann-Ganz catheter was placed, and initial parameters were central venous pressure 16 mmHg, pulmonary artery pressure 36/19 mmHg, systemic vascular resistance 574 Ds/cm^5, cardiac index 4.31 L/min/m^2, on dopamine at 10 mcg/kg/min. A bedside echocardiogram demonstrated severe global hypokinesis, with LVEF of 30%. A dobutamine infusion at 10 mcg/kg/min was added at this point to support cardiac contractility. Initial laboratory values on ICU admission included a normal complete blood count except a white cell count of 13.6x10^9/L, normal basic chemistry panel except glucose of 201 mg/dL, and troponin I of 1.4ng/mL. Over the next six hours, the patient's fraction of inhaled oxygen was weaned, and his vital signs stabilized. Systemic vascular resistance and cardiac output progressively increased and the dopamine and dobutamine infusions were gradually tapered off. Troponin I peaked at 7.3 ng/mL approximately 10 hours after the arrest, and declined thereafter. Eighteen hours after the initial arrest, a repeat echocardiogram demonstrated much improved cardiac contractility, with an LVEF of 50%, though still on low dose dobutamine. Twenty-four hours after the initial arrest, oxygenation had improved, and vital signs were stable. Chest radiograph demonstrated decreased pulmonary edema, and ECG demonstrated increase in QRS voltages to the patient's baseline, with return of his previous QRS axis, and shortening of the PR interval to within normal limits. Both pressor agents had been discontinued, and the patient was extubated.

FIG 1

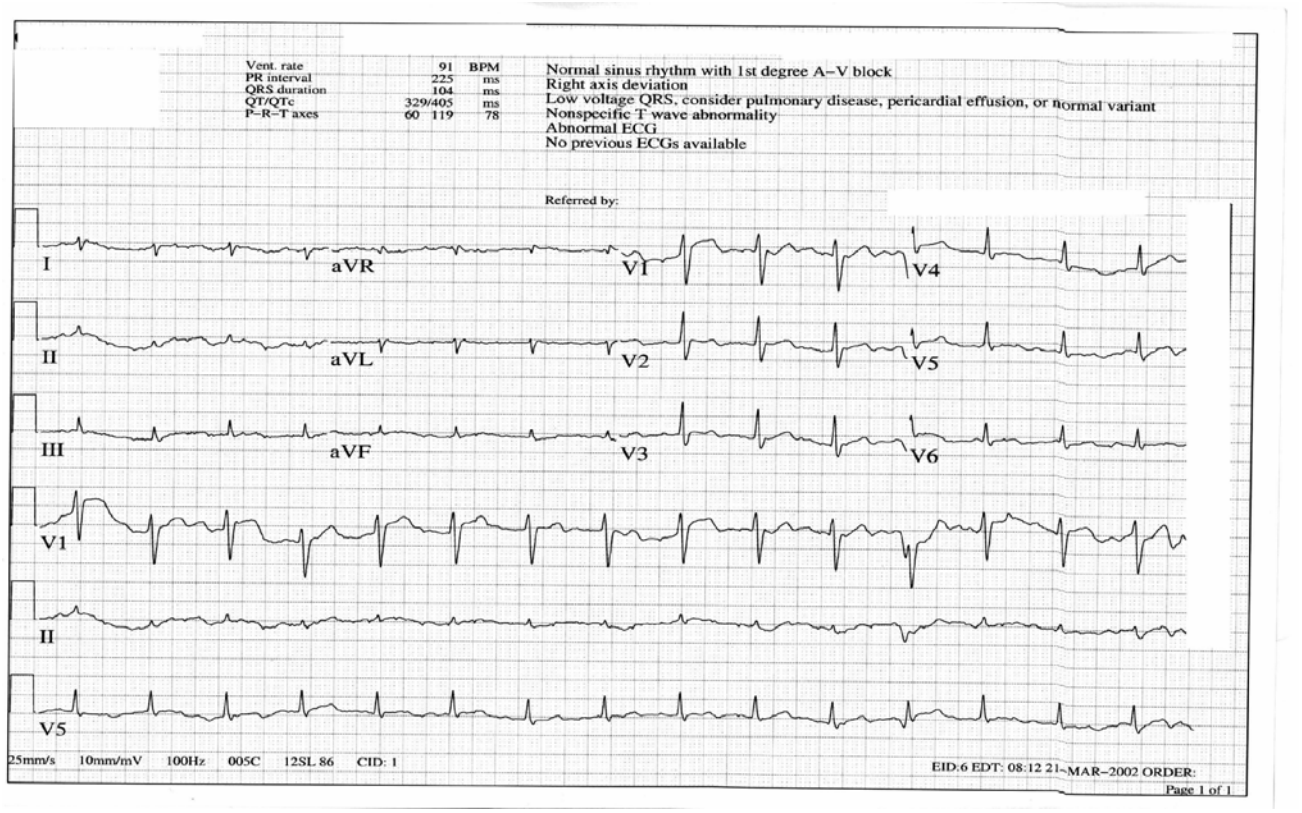
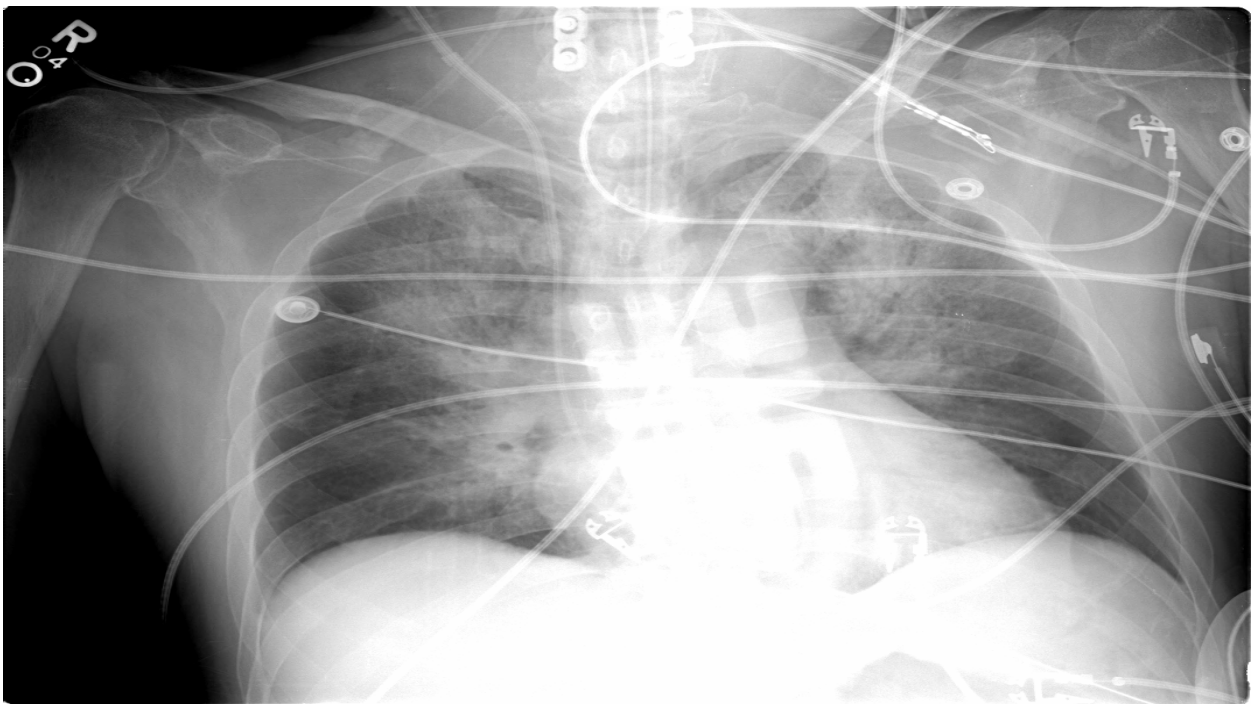


FIG 2



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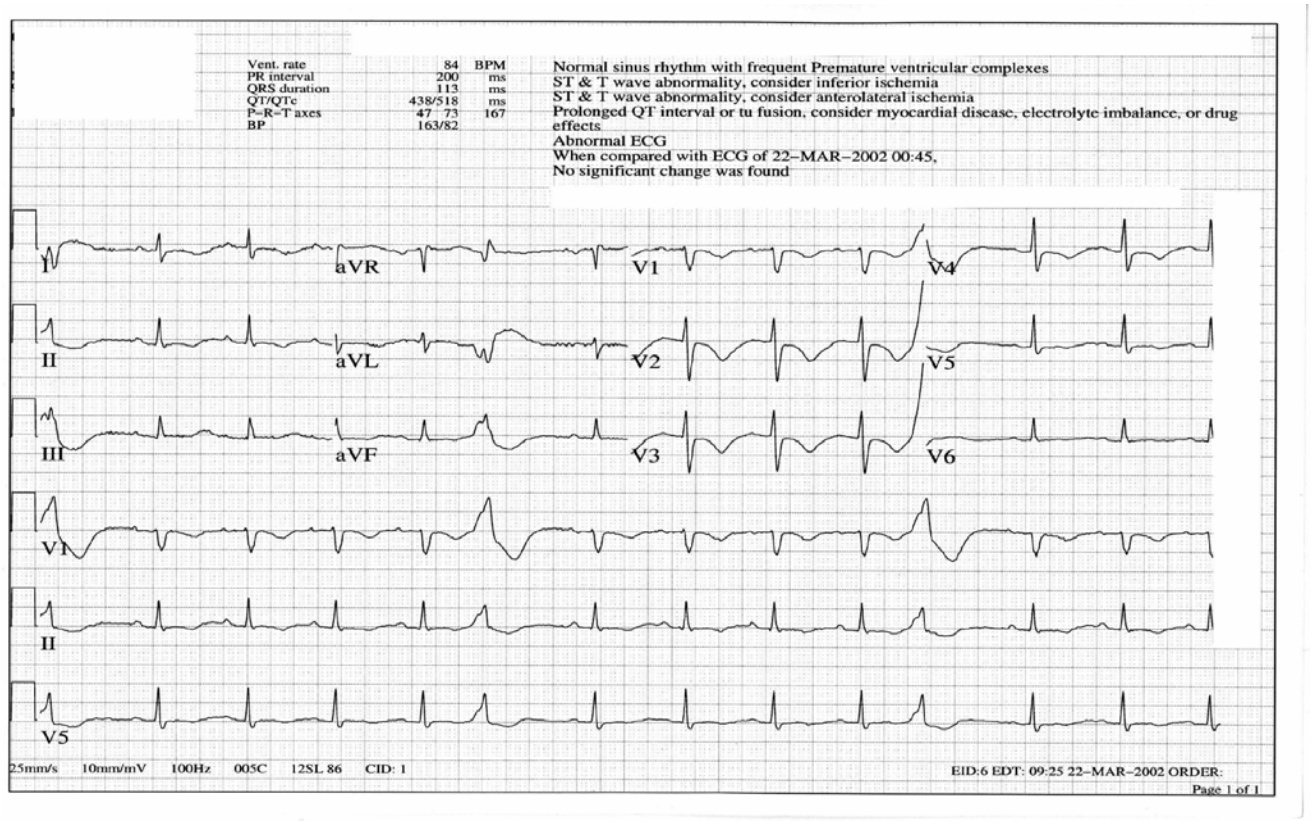
The next morning, approximately 42 hours after the initial arrest, the patient complained of crushing substernal chest pain. Vital signs were blood pressure 153/67 mmHg, pulse 87 beats per minute, respiratory rate 20 per minute, temperature 100°F, and SpO_2 98% on 2 liters of oxygen by nasal canula. An ECG was done, which is shown in figure 3. The new tracing showed symmetrically inverted T-waves in across the anterior precordium, concerning for left anterior descending coronary artery disease. Chest radiograph demonstrated further decrease in the pulmonary edema, and no new pathologic findings. The patient was treated with sublingual nitroglycerin, chewable aspirin, and nitroglycerin intravenous infusion, which rendered him pain free. Intravenous metoprolol was given and intravenous heparin was administered. The patient was taken emergently to the cardiac catheterization laboratory. Coronary angiography revealed no obstructive coronary disease, or lesion to correlate with the ECG findings. The patient remained stable and chest pain free for the remainder of his hospital course. The inverted T-waves, however, persisted on an ECG tracing done on the day of hospital discharge. He was transferred to the step-down unit on hospital day four, and discharged home in stable condition on hospital day six. Follow up electrocardiogram done in the outpatient setting seven months later demonstrated resolution of the T-wave inversions.

FIG 3



DISCUSSION

Local anesthetics are ubiquitous in modern medical procedures. Though the incidence of reported adverse effects of local anesthetics is low, occasional severe toxic effects and deaths have been reported.[1] Though central nervous system toxicity typically occurs more frequently and at lower serum concentrations of local anesthetics than does cardiotoxicity,[2] bupivacaine is known to be among the agents more likely to cause cardiotoxicity,[3] and was found in animal studies to be 4 to16 times more cardiotoxic than lidocaine.[4]

This case is novel in that the dose of bupivacaine the patient received was less than 1.1 mg/kg, whereas the minimum intravenous dose to produce toxicity commonly quoted is 1.6 mg/kg.[5,6] There are several possible explanations for this. First, though the bupivacaine was presumably injected intravascularly, the other factors with respect to the injection, such as the injection rate are not known. Perhaps the location of the injection, targeted for the lumbar sympathetic chain, may play a role. Also, the dose may have been given more rapidly than those used in previous studies of toxicity. Drug-drug interactions may also have contributed. The patient was taking the unusual combination of amitriptyline and carbamazepine as an outpatient for his chronic back pain. Each of those medications has known cardiotoxicity potential,[7,8] and perhaps they may have interacted in some way to lower the threshold of toxicity for bupivacaine. Local anesthetics are known to depress the maximum rate of increase of the cardiac action potential. Bupivicaine binds to inactivated sodium channels on the myocardium and dissociates slowly from these channels.[9] The combination of bupivicaine and a tricyclic antidepressant in a susceptible individual might theoretically cause the outcomes observed in our patient. Furthermore, local anesthetic dysrhythmogenic properties are thought to be related to the compounds' interference with membrane ion conduction, which can cause myocardial depression. This is thought to be due to impairment of mitochondrial energy transduction via uncoupling of oxidative phophorylation and the inhibition of complex 1 in the mitochondrial respiratory chain.[10] The role, if any, which the patient's procedural sedation by propofol infusion played, is uncertain. Propofol is known to cause bradydysrhythmias and hypotension,[11] and thus might have potentiated the effects of bupivacaine. Conversely, however, animal studies have demonstrated that propofol infusion increases the minimum toxic dose of intravenous bupivacaine.[12]

It is interesting to note that the patient's echocardiogram and Swan-Ganz catheter data are not consistent with purely cardiogenic shock.[13] Whereas in cardiogenic shock, an increased systemic vascular resistance would be expected to compensate for low cardiac out, the patient in our case had a low SVR, despite a vasopressor-dose dopamine infusion. This suggests a significant component of distributive shock. Local anesthetics are known for their propensity to change peripheral vascular tone, and these effects can be related to intravascular concentration.[14,15]

Globally depressed LV contractility, as seen by echocardiography, has been documented in controlled bupivacaine toxicity in dogs,[16] and in human volunteers.[17] Although not specifically noted on our patient's echocardiogram, perhaps a phenomenon related to the RV enlargement described in the same animal study may explain our patient's initial rightward QRS axis on ECG. The initial electrocardiographic finding of new first degree AV block, has been previously described; QRS widening, though often described in bupivacaine toxicity, was not seen in this case.[15] The globally depressed voltage of the QRS complexes on the initial EKG, though previously described in pigs,[18] is not a typically described feature of bupivacaine toxicity in humans, and the mechanism for this finding is unknown. The delayed onset of symmetrically inverted T-waves anteriorly is also unexplained. Their coincidental appearance with a chest pain syndrome, with no significant coronary disease on angiography, is similarly enigmatic. Repolarization changes associated with bupivacaine have been previously described,[19] however we found no previous report of an ECG morphology similar to our patient's in a similar clinical situation.

CONCLUSION

We present a case of bupivacaine-induced cardiovascular collapse with several novel features. First, our patient's toxicologic insult was a relatively low dose of bupivacaine, at less than 1.1 mg/kg. Second, his shock physiology was that of mixed cardiogenic and distributive shock. Finally, he developed an unexplained delayed EKG finding, symmetrically inverted anterior T-waves, which resolved with time. The role that propofol procedural sedation may have played in these findings is unknown. Though bupivacaine will remain a first-line agent for local anesthesia for the foreseeable future, clinicians should be vigilant when using this agent, and should be prepared to treat toxicity with aggressive supportive care**.**

REFERENCES

1. Moore DC, Bridenbaugh LD, Thompson GE, Balfour RI, Horton WG. Bupivacaine: A review of 11,080 cases. Anesth. Analg. 1978, 57 (1), 42-53.
2. Brown DL, Ransom DM, Hall JA, Leicht CH, Schroeder DR, Offord KP. Regional anesthesia and local anesthetic-induced systemic toxicity: seizure frequency and accompanying cardiovascular changes. Anesth. Analg. 1995, 81 (2), 321-328.
3. Morishima HO, Pedersen H, Finster M, Hiraoka H, Tsuji A, Feldman HS, Arthur GR, Covino BG. Bupivacaine toxicity in pregnant and nonpregnant ewes. Anesthesiology. 1985, 63 (2), 134-139.
4. Reiz S, Nath S. Cardiotoxicity of local anesthetic agents. Br. J. Anaesth. 1986, 58 (7), 736-746.
5. Durrani Z, Winnie AP. Brainstem toxicity with reversible locked-in syndrome after intrascalene brachial plexus block. Anesth Analg. 1991, 72 (2) 249-252.
6. Carpenter RL, Mackey DC. Local Anesthetics. In Clinical Anesthesia, 3rd Ed.; Barash PG, Cullen BF, Stoelting RK. Eds.; Lippincott-Raven: Philadelphia, 1997; 413-440.
7. Apfelbaum JD, Caravati EM, Kerns WP, Bossart PJ, Larsen G. Cardiovascular effects of carbamazepine toxicity. Ann Emerg Med. 1995, 25 (5), 631-635.
8. Mokhlesi B, Leikin JB, Murray P, Corbridge TC. Adult Toxicology in Critical Care, Part II: Specific Poisonings. Chest. 2003, 123 (3), 897-922.
9. Clarkson C, Hondeghem LM. Mechanism for bupivicaine depression of cardiac conduction: Fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology 1985;62:396-405.
10. Sztark F, Malgat M, Dabadie P, et. al. Comparison of the effects of bupivicaine and ropivicaine on heart cell mitochondrial bioenergetics. Anesthesiology 1998;88:1340-1349.
11. Reves JG, Glass PSA, Lubarsky DA. Nonbarbiturate Intravenous Anesthetics – Propofol. In Anesthesia, 5th Ed.; Miller, R.D., Ed.; Churchill Livingstone: Philadelphia, 2000; 249-256.
12. Ohmura S, Ohta T, Yamamoto K, Kobayashi T. A comparison of the effects of propofol and sevoflurane on the systemic toxicity of intravenous bupivacaine in rats. Anesth. Analg. 1999, 88 (1) 155-159.
13. Kumar A, Parillo JE. Shock: Classification, Pathophysiology, and Approach to Management. In Critical Care Medicine: Principals of Diagnosis and Management in the Adult, 2nd Ed. Parillo JE; Dellinger RP, Eds.; Mosby: St. Louis, 2002; 371-420.
14. Pickering AE, Hidefumi W, Headley PM, Paton JFR. Investigation of systemic bupivacaine toxicity using the in situ perfused working heart-brainstem preparation of the rat. Anesthesiology. 2002, 97 (6) 1550-1556.
15. Berde CB, Strichartz GR. Local Anesthetics. In Anesthesia, 5th Ed.; Miller, RD., Ed.; Churchill Livingstone: Philadelphia, 2000; 491-521.
16. Coyle DE, Porembka DT, Sehlhorst CS, Wan L, Behbehani MM. Echocardiographic evaluation of bupivacaine cardiotoxicity. Anesth. Analg. 1994, 79 (2), 335-339.
17. Knudsen K, Suurkula MB, 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 (5), 507-514.
18. Nystrom EU, Heavner JE, Buffington CW. Blood Pressure Is Maintained Despite Profound Myocardial Depression During Acute Bupivacaine Overdose in Pigs. Anesth. Analg. 1999, 85 (8), 1143-1148.
19. Phillips N, Priestly M, Denniss AR, Uther JB. Brugada-type Electrocardiographic pattern induced by epidural bupivacaine. Anesth. Analg. 2003, 97 (1), 264-267.