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Bupivacaine-induced Cardiac Toxicity in Neonates: Successful Treatment with Intravenous Phenytoin

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REGIONAL anesthesia is increasingly being used in children as a component of intra- and postoperative anesthetic management.[1] Advantages of regional anesthesia include a reduction of general anesthetic requirements, rapid emergence from anesthesia, and excellent intra- and postoperative analgesia.[1] Complications related to local anesthetic toxicity in children are rare and are usually caused by unintended intravenous administration or by accumulation of excessive amounts of drug administered either by repeated bolus dosing or by continuous infusion.[2–4] Cardiovascular toxicity due to bupivacaine is the most feared complication because it presents as ventricular dysrhythmias that may be refractory to treatment.

We describe two newborns (one of whom has been described previously[4]) who developed cardiac dysrhythmias while receiving epidural bupivacaine either by continuous infusion or by repeated bolus dosing. In both cases, the dysrhythmias were successfully treated with intravenous phenytoin after other therapies, including bretylium, had been unsuccessful.

Case Reports

Case 1

The patient was a full-term, 3,890-g boy born with exstrophy of the bladder who underwent surgical correction at 24 h of age. After induction of general tracheal anesthesia with halothane, nitrous oxide, oxygen, and pancuronium, a 20-G epidural catheter was inserted into the caudal space. A bolus of 1 $ml \cdot kg^{-1}$ (2.5 $mg \cdot kg^{-1}$) 0.25% bupivacaine with epinephrine (5 $\mu g \cdot ml^{-1}$) was administered through the catheter. Efficacy of blockade was demonstrated by decreased general anesthetic requirements. The patient received supplemental doses of 0.25% bupivacaine with epinephrine (5 $\mu g \cdot ml^{-1}$) of 1.87 $mg \cdot kg^{-1}$ (× 2) 90 and 180 min after the initial dose. After completion of the uneventful operative repair, the trachea was extubated, and the patient was transferred to the pediatric intensive care unit.

A continuous infusion of 0.25% bupivacaine with epinephrine (5 $\mu g \cdot ml^{-1}$) of 1 $ml \cdot kg^{-1} \cdot h^{-1}$ (2.5 $mg \cdot kg^{-1} \cdot h^{-1}$) was started in the pediatric intensive care unit 90 min after the last intraoperative dose. At that time, a normal sinus rhythm of 120 beats/min was present (fig. 1A). Ten hours after the infusion was begun, bigeminy developed suddenly and deteriorated into wide-complex tachydysrhythmia (figs. 1B and 1C). The patient's heart rate was 140 beats/min, and blood pressure was 45/25 mmHg. Advanced cardiac life support, including oral tracheal intubation, epinephrine 10 $\mu g \cdot kg^{-1}$ (× 2), and sodium bicarbonate 1 $mEq \cdot kg^{-1}$, resulted in a ventricular tachycardia with a rate of 200 beats/min and a blood pressure of 75/40 mmHg. The bupivacaine infusion was stopped, and lidocaine (1 $mg \cdot kg^{-1}$) was administered (× 3) followed by a lidocaine infusion of 30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without a change in rhythm. The patient then received phenytoin 5 $mg \cdot kg^{-1}$ (× 2, slow bolus) with rapid conversion to a normal sinus rhythm (fig. 1D).

Approximately 2 h later, the patient's rhythm spontaneously reverted to ventricular tachycardia with a rate of 160 beats/min and a blood pressure of 70/40 mmHg (fig. 1E). Bretylium (5 $mg \cdot kg^{-1}$) was administered × 2 without change in rhythm (fig. 1F). Tonic-clonic seizures occurred. Diazepam (0.25 $mg \cdot kg^{-1}$ intravenous) and phenytoin (7 $mg \cdot kg^{-1}$ total) were administered in divided doses and resulted in conversion to a normal sinus rhythm (fig. 1G) and cessation of seizure activity.

The patient subsequently had no further dysrhythmia, and the trachea was successfully extubated without apparent sequelae. Serum bupivacaine concentrations measured in blood samples drawn immediately after the first dysrhythmia and 12 h later were 5.6 and 3.7 $\mu g \cdot ml^{-1}$, respectively.

Case 2

The patient was a full-term, 4,400-g boy born with exstrophy of the bladder. He was taken to the operating room for surgical repair at 2 weeks of age. General tracheal anesthesia was induced and maintained with halothane, nitrous oxide, oxygen, and pancuronium. A 20-G epidural catheter was inserted into the caudal space, and

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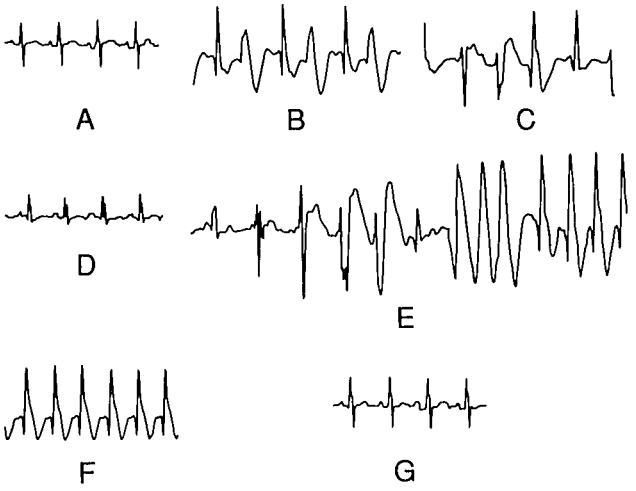

Fig. 1. Bupivacaine-induced dysrhythmia and resolution after intravenous phenytoin in patient 1. (*A*) Normal sinus rhythm at 120 beats/min. (*B*) Bigeminy at a rate of approximately 140 beats/min that (*C*) deteriorated into a wide-complex tachydysrhythmia. (*D*) after intravenous phenytoin, rapid conversion to a normal sinus rhythm. (*E*) Ventricular tachycardia with a rate of 160 beats/min. (*F*) Ventricular tachycardia unchanged after intravenous bretylium. (*G*) Conversion to normal sinus rhythm after phenytoin.

blockade was initiated with 1 $ml \cdot kg^{-1}$ (2.5 $mg \cdot kg^{-1}$) 0.25% bupivacaine with epinephrine (5 $\mu g \cdot ml^{-1}$). Approximately 150 min later, the patient received a second dose of 0.125% bupivacaine, 1 $ml \cdot kg^{-1}$ (1.25 $mg \cdot kg^{-1}$) with epinephrine (5 $\mu g \cdot ml^{-1}$). Two hours later, the patient received a third dose of 0.25% bupivacaine, 0.7 $ml \cdot kg^{-1}$ (1.75 $mg \cdot kg^{-1}$), with epinephrine (5 $\mu g \cdot ml^{-1}$), without immediate change in heart rate or blood pressure (fig. 2A).

Five minutes later, a sudden-onset, wide-complex tachydysrhythmia with a rate of 120 beats/min (fig. 2B) and a blood pressure of 90/60 mmHg developed. All anesthetic agents were discontinued, and 100% oxygen was administered. After bretylium (5 $mg \cdot kg^{-1}$) was administered (× 2), the heart rate increased to 240 beats/min and blood pressure decreased to 65/40 mmHg (fig. 2C). Phenytoin (7 $mg \cdot kg^{-1}$) in divided doses was followed by conversion to a normal sinus rhythm (fig. 2D).

The procedure was completed shortly thereafter and the patient was transported to the pediatric intensive care unit for postoperative care. His trachea was extubated upon arrival in the pediatric intensive care unit, and he was discharged to the pediatric ward 24 h later without apparent sequelae. Unfortunately, the blood specimen sent for determination of bupivacaine concentration was lost.

Discussion

We report the successful treatment of bupivacaine-induced cardiac dysrhythmias with phenytoin in two full-term newborns after other therapies, including bretylium, had been unsuccessful. Both patients experienced toxicity. The first patient received an excessive amount of bupivacaine by epidural infusion. The second patient received bolus doses of bupivacaine, which had not been associated with local anesthetic toxicity in older children. The doses that caused toxicity in the second patient were the result of our initial attempts to apply our successful intra- and postoperative methods in older children to neonates. The infusion rate the first patient received was excessive even by that standard.

Neonates may be at increased risk for bupivacaine toxicity. First, young infants (less than 3 months of age) have low liver blood flow and immature metabolic pathways. Thus, larger fractions of amide local anesthetics are not metabolized and remain active in the plasma.[5,6] Second, neonates have lower concentrations of albumin and α_1-acid glycoproteins,[7] leading to increased concentrations of unbound drug. The larger volume of distribution at steady state in the neonate may confer some clinical protection by reducing plasma drug concentrations after bolus administration.[8] In animals, the studies evaluating the effect of age on dose–response relationships of bupivacaine toxicity have been limited and the results inconsistent.[9,10] Finally, the ability to detect toxicity in these patients is decreased because signs of central nervous system irritability that may precede the onset of dysrhythmias or seizures may be difficult to recognize because of an inability to communicate (due to the young age) or because of unconsciousness (due to general anesthesia). The blood concentration at which bupivacaine toxicity occurs in newborns is unknown. The bupivacaine concentration (5.6 $\mu g \cdot ml^{-1}$) in case 1 was in the range associated with cardiovascular toxicity in adults (greater than 4 $\mu g \cdot ml^{-1}$).[11,12]

Factors reported to increase bupivacaine toxicity include hypoxia, acidosis, hyponatremia, and hyperka-

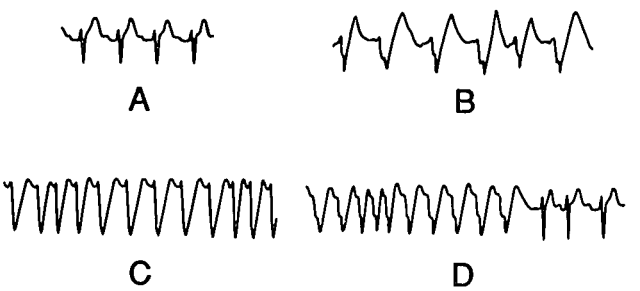

Fig. 2. Bupivacaine-induced dysrhythmia and resolution after intravenous phenytoin in patient 2. (*A*) Normal sinus rhythm. (*B*) wide-complex tachydysrhythmia with a rate of 120 beats/min. (*C*) wide-complex tachydysrhythmia with rate increasing to 240 beats/min after intravenous bretylium. (*D*) Conversion to a normal sinus rhythm after intravenous phenytoin.

lemia.[13-15] Experimentally, plasma bupivacaine concentrations increased in animals receiving halothane. This increase was attributed to decreased liver blood flow associated with halothane-induced hypotension.[7] It is unknown whether this pharmacokinetic effect occurs in human infants receiving halothane in the clinical situation, in which vagolytic drugs along with fluid administration support heart rate and blood pressure. It is also unknown whether bupivacaine metabolism is slowed by halothane administration in the absence of hypotension.

As in our patients, bupivacaine solutions frequently contain epinephrine ($5\ \mu g \cdot ml^{-1}$), not only in the "test dose" but in every dose given. In spontaneously breathing pigs, the addition of epinephrine did not change the dose of bupivacaine causing cardiovascular collapse, although it decreased the dose at which seizures and dysrhythmias occurred.[16] Epinephrine appeared to reduce the doses causing seizures and dysrhythmias by vasoconstriction and reduction of distribution volume. This is supported by the observation that the plasma bupivacaine concentrations at which the seizures and dysrhythmias occurred were the same, despite the lower dose administered.

The mechanism of action of bupivacaine, blockade of fast sodium ion channels in the plasma membrane, results in both its therapeutic and its toxic effects. Its duration of action in the nerve cell membrane and the entire cardiac conducting system is greater than that of lidocaine because of its greater affinity for sodium channels. Because bupivacaine dissociates from the cardiac sodium channel more slowly than does lidocaine, it slows conduction at lower heart rates.[17] Slowing of the action potential in the Purkinje system prolongs the QRS and QT intervals and thereby increases the likelihood of reentrant rhythm, which may be either ventricular or supraventricular with aberrant conduction (both "wide-complex"). High-resolution ventricular epicardial mapping in rabbit hearts has provided the first direct evidence of reentrant ventricular dysrhythmias *via* prolongation of ventricular effective refractory period and slowed conduction velocity in a dose- and use-dependent manner.[18]

In addition to the direct effects of intravenous bupivacaine on the myocardium and conducting system,[8,9,19] direct central nervous system mechanisms of bupivacaine-induced dysrhythmias have been identified. Very small doses of bupivacaine administered intracerebrally or intraventricularly have produced the same cardiac dysrhythmias seen with the administration of toxic doses intravenously.[20,21] The mechanism of these central nervous system effects is thought to be blockade of γ-aminobutyric acid–ergic neurons that tonically inhibit the autonomic nervous system,[12] because either an intraventricularly administered γ-aminobutyric acid potentiator (midazolam) or peripheral autonomic ganglion blocker (hexamethonium) has been shown to be capable of terminating bupivacaine-induced dysrhythmias.[12,22]

Bupivacaine-induced dysrhythmias have been refractory to treatment. Lidocaine, bretylium, magnesium, calcium channel blockers, and amiodarone have been used experimentally with variable results.[23-27] By binding to the same receptor, lidocaine at high doses may displace bupivacaine from cardiac sodium channels,[28] and has on occasion been successful in the resuscitation of humans.[12] Bretylium has been more effective than lidocaine in animals with experimental bupivacaine-induced dysrhythmias.[25,26] The unique antidysrhythmic mechanism of bretylium is related to blockade of norepinephrine reuptake as well as blockade of potassium channels, which together prolong repolarization.[29] Despite the experimental efficacy of bretylium in the treatment of bupivacaine-induced cardiac toxicity, there have been no reports of its successful clinical use in humans. Indeed, bretylium was administered to both patients described in this report and failed to convert the dysrhythmias.

The use of phenytoin for the treatment of bupivacaine-induced dysrhythmias either clinically or experimentally has not been previously reported, although it has been used for seizure control in a patient who had both seizures and cardiac toxicity.[12] Phenytoin is a class 1_B antidysrhythmic agent that hastens membrane repolarization while decreasing the slope of phase 4 depolarization in Purkinje fibers. It acts to decrease the duration of the action potential of the Purkinje fiber.[30] Phenytoin interacts with fast sodium channels to reduce sodium ion currents during action potentials in a fashion similar to that of lidocaine.[31] It may therefore bind to the same receptor as lidocaine and therefore might be expected to displace bupivacaine, thereby terminating the dysrhythmia. Unlike lidocaine, also a class 1_B agent, phenytoin has been shown to block cardiac calcium channels.[32] This mechanism may account for its effectiveness against dysrhythmias associated with digitalis toxicity.[33] It is also possible that phenytoin may be a very effective treatment for bupivacaine-induced dysrhythmias because of its effects on the autonomic control centers in the brain, which may coun-

teract the autonomically mediated effects of bupivacaine described above.[15,16] Specifically, phenytoin modulates both vagal and cardiac sympathetic efferent activity.[29]

Phenytoin should be diluted in normal saline and administered slowly (at a rate not to exceed 50 $mg \cdot min^{-1}$) through a freely flowing intravenous catheter. The initial dose should be 5 $mg \cdot kg^{-1}$; second and third doses may be administered as necessary at 5-min intervals, to a maximum dose of 15 $mg \cdot kg^{-1}$.[25]

We report our initial experience in neonates with epidural anesthesia with repeated doses or continuous infusion of bupivacaine. Our two patients appeared to have received toxic doses. Increased experience with bupivacaine infusions in infants will allow practitioners to choose the lowest effective infusion rate. Currently, we use bupivacaine in neonates only for the first intraoperative bolus. Because lidocaine can easily be measured in most hospital clinical laboratories and because it is less cardiotoxic than bupivacaine, we now prefer it for continuous local anesthetic infusions or for supplemental doses in neonates and young infants. If bupivacaine is used and cardiac dysrhythmias develop, phenytoin should be added to the small list of drugs that may have the potential to reverse bupivacaine-induced cardiac toxicity.

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Normal Activated Clotting Time Despite Adequate Anticoagulation with Ancrod in a Patient with Heparin-associated Thrombocytopenia and Thrombosis Undergoing Cardiopulmonary Bypass

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ANCROD (Arvin, Knoll Pharmaceutical, Whippany, NJ), is a defibrinogenating enzyme purified from the venom of the Malayan pit viper (*Agkistrodon rhodostoma*). Ancrod has been proposed as an alternative to heparin for anticoagulation in patients with thromboembolic disorders and in patients with contraindications to heparin during cardiopulmonary bypass (CPB).[1,2] It is usually administered as a continuous infusion preoperatively and titrated to achieve plasma fibrinogen concentrations of 0.2–0.7 g/l to ensure adequate anticoagulation and to prevent thrombus in the extracorporeal circuit during CPB. The activated clotting time (ACT) is routinely used to ensure adequate anticoagulation when heparin is used for anticoagulation for bypass.

Very little information has been published, however, on the optimal method for ensuring adequate anticoagulation in patients receiving ancrod for anticoagulation during CPB. In particular, the effect of ancrod-induced hypofibrinogenemia on the ACT has not been well characterized.[1] We describe a patient undergoing CPB with ancrod anticoagulation who, despite documented hypofibrinogenemia (0.33 g/l), maintained normal ACT values before CPB.

Case Report

A 73-year-old man was referred to the University of Virginia Health Sciences Center for cardiac catheterization and possible coronary artery bypass grafting. His past medical history was significant for heparin-associated thrombocytopenia and thrombosis. In 1989 the patient had sustained a pelvic fracture, which was complicated by left leg deep vein thrombosis during hospitalization. After initiation of heparin therapy, he had developed thrombocytopenia and arterial thrombosis, resulting in ischemia of his left foot and requiring amputation of the lateral three toes.

The patient was admitted with unstable angina. Because of the history of heparin-associated thrombocytopenia and thrombosis, the patient was a candidate for the use of ancrod under a compassionate-use protocol approved by the Human Investigation Committee. An intravenous infusion of ancrod was begun, and the patient underwent cardiac catheterization without complication. The ancrod infusion was continued until the morning of surgery. One hour preoperatively, the fibrinogen concentration (0.35 g/l) was within the therapeutic range. The ancrod infusion was discontinued immediately before uneventful induction of anesthesia with sufentanil. Before cannulation

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