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Bupivacaine Toxicity Secondary to Continuous Cervical Epidural Infusion

Case Report

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Background and Objectives. A case is described of bupivacaine toxicity after continuous cervical epidural infusion in a patient with intractable cancer pain. The patient had several periods of generalized tonic clonic seizures. Serial venous blood samples were taken after the first signs of toxicity. The highest total plasma bupivacaine level was 20.3 μg/mL. The corresponding free bupivacaine concentration was not determined. The highest measured free bupivacaine concentration was 1.21 μg/mL, corresponding with a total plasma bupivacaine level of 6.7 μg/mL. There were no signs of cardiovascular toxicity. The patient recovered after treatment without adverse sequelae. *Methods.* A plasma concentration–time curve was constructed. There was a rise in the plasma concentration of bupivacaine after the continuous infusion was stopped. *Results.* Total body clearance of bupivacaine was 20 mL/min and elimination half-life was 27 hours. *Conclusions.* The case emphasizes the importance of serial plasma concentrations of bupivacaine after continuous epidural infusion and the value of free bupivacaine concentration versus total bupivacaine concentration. *Reg Anesth 1995: 20: 163–168.*

Key words: bupivacaine, continuous cervical epidural infusion, systematic accumulation, toxic effects, total body clearance.

There are some patients with cancer pain in whom pain control is very difficult, because some pain syndromes may approach the nociceptive stimulation levels of surgical or postoperative pain. Therefore, the use of regional local anesthetics may be indicated.[1]

Case Report

A 51-year-old woman, weighing 50 kg, with a history of heavy smoking and high alcohol consumption, underwent a partial mandibulectomy and neck dissection because of a squamous cell carcinoma of the left inferior processus alveolaris (TNM classification: T4N2bM0).

After the operation, there were no functional problems such as difficulty with speech or swallowing, and radiotherapy was started (total dose 64 Gy). Immediately after the radiation therapy was finished, the patient complained of severe pain in the neck on the operated and radiated side. There was profound spasticity on the left side of the neck, shoulder, and upper limb. There were no signs of recurrence of the primary tumor. Current medication consisted of oxazepam 50 mg, twice daily; temazepam 20 mg, once daily; and ranitidine 150 mg, twice daily.

Previous pain treatment included the use of sustained release morphine, coanalgesic therapy (acetaminophen, NSAID), benzodiazepines, and transcutaneous electric nerve stimulation (TENS).

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Failure to achieve acceptable pain relief and the uncontrollable side effects of morphine resulted in the choice of continuous cervical epidural infusion of bupivacaine for pain treatment.

A cervical epidural catheter was inserted at level C7–T1 using the paramedian approach (18-gauge Tuohy needle, hanging-drop technique). This level was chosen because it corresponded with the segmental spinal cord level of maximal nociceptive pain stimulation. A bolus of 3 mL bupivacaine 0.5% with epinephrine 1:200,000 was injected through the catheter. This resulted in a symmetric segmental sensory analgesia level of C3–T1 with only minimal motor block (grade I).[2]

The initial bolus was followed by a continuous epidural infusion of bupivacaine 0.75% without epinephrine at an infusion rate of 1.8 mL/h (13.5 mg/h). With this regimen the patient was pain free (visual analog scale = 0). Respiratory rate, arterial pressure, and heart rate were stable. The patient was visited daily by an anesthesiologist. Six months before the operation, the patient had been treated in the same way with a lower dose (infusion rate of 1.0 mL/h, 7.5 mg/h), resulting in satisfactory analgesia. After satisfactory analgesia was accomplished clinically, the patient returned home and was treated with continuous epidural infusion of bupivacaine for 10 days using a Pharmacia Deltec CADD-PCA Pump (Pharmacia, Uppsala, Sweden).

On the evening of the third day, 53.5 hours after starting the continuous infusion of bupivacaine, the patient's condition deteriorated suddenly. The patient had tonic clonic seizures lasting about 1 minute. The seizures were followed by increased lethargy. Her vital signs, including respiratory rate, arterial pressure, and heart rate, remained stable. There was no evidence of hypoxia or postictal apnea.

The epidural infusion of bupivacaine was stopped immediately. The position of the catheter was assessed by careful aspiration. There were no signs of intravenous or subarachnoid migration of the catheter tip. Sensory anesthesia was tested by pinprick and revealed a symmetric segmental sensory analgesia level of dermatomes C7–T2 with a bilateral motor block (grade III)[2] of the upper limbs. The patient received diazepam 10 mg rectally and no further seizures occurred. Electrolytes, calcium, magnesium, glucose and liver, and renal function tests were normal. The total plasma bupivacaine concentration was 10.7 μg/mL.

At that time the patient had received 737 mg bupivacaine over 53.5 hours. Further bupivacaine venous blood samples were taken 2, 11, and 43 hours after the first insult (Table 1). Oral carbamazepine 200 mg, three times daily, and amitriptyline 25 mg, once daily, were started for pain relief. Neurologic examination after the seizures revealed no abnormalities.

Forty-two hours after the first insult, the continuous infusion of bupivacaine was started again because the patient complained of unbearable pain and had suicidal thoughts. After a bolus of 3 mL bupivacaine 0.5% with epinephrine 1:200,000 was administered, a continuous infusion of bupivacaine 0.75% without epinephrine was started at an infusion rate of 1.0 mL/h (7.5 mg/h). This resulted in a sensory analgesia level of dermatomes C3–T4 with good pain relief. Twenty-one hours later, the patient again had a tonic clonic seizure after an infusion of 172 mg bupivacaine over that period. The infusion of bupivacaine was stopped and the catheter tip position reassessed. The patient was treated in the same way with diazepam 10 mg rectally and clonazepam 0.5 mg intramuscular twice daily. Venous blood samples were taken immediately after the insult and 9, 21, 45, and 69 hours later (Table 1). A computer tomography scan of the cerebrum was normal and showed no metastatic lesions.

After the second insult, the patient had three more periods with seizures. An ECG was done each time but showed no abnormalities. Two times she fell while she was on her way to the bathroom. The patient reported no prodromal signs usually seen with acute systemic toxicity of local anesthetics. The cervical epidural catheter was removed. Block of the cervical nerves C2–3 was achieved with local anesthetic injections; this clearly reduced the pain and the patient was allowed to return home.

Materials and Methods

Bupivacaine analysis was performed using the high-performance liquid chromatography (HPLC) method as described.[3]

Reagents and Materials

Bupivacaine HCl (Astra Pharmaceutics, Rijswijk, The Netherlands) was used for the epidural infusion. Solvents were of HPLC grade. A stock solution of 200 mg/L was prepared in 100% methanol. Drug plasma standards were prepared by spiking blank control plasma with appropriate microliter volumes of working drug solution. Six plasma standards were obtained with the following concentrations of bupivacaine: 0.25, 1.0, 2.0, 4.0, 10.0, and 25 μg/mL.

Preparation of the Samples

Twenty micrograms of bupivacaine in 180 μL of blank plasma or 200 μg sample plasma and 200 μg

Table 1. Unbound and Total Plasma Bupivacaine Concentrations in a Patient Receiving Continuous Cervical Epidural Bupivacaine Infusion

Hours After Starting the Continuous Infusion	Total Plasma Bupivacaine (μg/mL)	Free Bupivacaine (μg/mL)	Bound (%)	Total Amount of Infused Bupivacaine (mg)	Clinical Presentation	Infusion Rate (mg/h)
53.5	10.7	Not determined		737.25	Seizures	13.5
55.5	20.3	Not determined				0
66.5	17.7	Not determined				0
97	8.3	0.80	90			After 109.5 h infusion was restarted at rate 7.5
114.5	4.3	0.80	81	172.5	Seizures	0
123.5	5.3	1.12	79		Seizures	0
136	6.7	1.21	82		Seizures	0
160	5.1	0.66	87			0
184	3.2	0.75	77			0

Average protein binding, 85% (±5%).

trichloroacetic acid were placed into a 1.5 mL Eppendorf tube (Eppendorf, Hamburg, Germany). After mixing and centrifuging at 12,500g for 4 minutes, 100 μL of the supernatant was injected onto the column.

High-performance Liquid Chromatography

The analysis was performed using a 740 solvent delivery system (Spectra Physics, Eindhoven, The Netherlands), a BD 40 recorder (Kipp Analytica, Delft, The Netherlands), an N 60 injector (Valco H, Chrompack, Middelburg, The Netherlands), a Spherisorb 5 ODS column (250 × 4.6 mm; Chrompack), and a Spectroflow 757 variable wavelength absorbance detector (Separations, H.I. Ambacht, The Netherlands). Detection was achieved at 217 nm. The mobile phase consisted of phosphoric acid 0.006 M, acetonitrile (65:35 vol/vol) and tetramethylammoniumchloride 0.750 g/L. The flow rate was 1.2 mL/minute. The retention time of bupivacaine is 13.0 minutes.

Free Bupivacaine Concentration

For determination of free bupivacaine concentration the Amicon Micropartition System (MPS-1, Amicon Division, Capelle a/d IJsel, The Netherlands) was used. Based on the unique equilibrium nature of ultrafiltration partition, it is intended for separation of free from protein bound microsolute in small volumes of serum, plasma, or other biological fluids at physiological pH of 7.4. Separation of free from protein bound microsolute is provided by convective filtration of free microsolute through an anisotropic, hydrophilic YMT ultrafiltration membrane. The driving force for filtration is provided by centrifugation during 15 minutes at 1,000–2,000 × g, achieving transmembrane pressures of up to 106 psi (7.2 atm). Use of a fixed-angle rotor provides polarization control, minimizing the potential for nonideal protein–protein interactions. The ultrafiltrate can then be analyzed for free microsolute fraction or concentration. The procedure is performed at room temperature.

Validation

The calibration curves were constructed by plotting the peak height ratios against known concentrations of bupivacaine. Standard curves were constructed by least-square regression for calculation of unknown concentrations. Interday variation is 8% CV (coefficient of variance) at 0.5 μg/mL and 1.5% CV at 4.0 μg/mL. Interday variation is 9.7% CV at 0.5 μg/mL, 4.6% CV at 1.0 μg/mL, 5.0% at 2.0 μg/mL, and 3.1% CV at 4.0 μg/mL.

Results

Systemic toxicity of bupivacaine with a total plasma level of 20.3 μg/mL without signs of cardiovascular toxicity has never been reported. The plasma concentration-time curve of our patient is shown in Figure 1. The total bupivacaine and free bupivacaine levels are listed in Table 1.

With the data from Table 1 and assuming a steady-state concentration (Css) of 10.7 μg/mL, the total body clearance can be calculated. The total body clearance is equal to the rate of infusion (Ro) divided by the steady-state plasma concentration.[3–6] The clearance of bupivacaine at the time of the first convulsion is 20 mL/min, which is extremely low. The calculated elimination half-life is 27 hours, which corresponds with an extremely low clearance. The sample taken at 53 hours is approximately 75% of the expected steady-state value and the

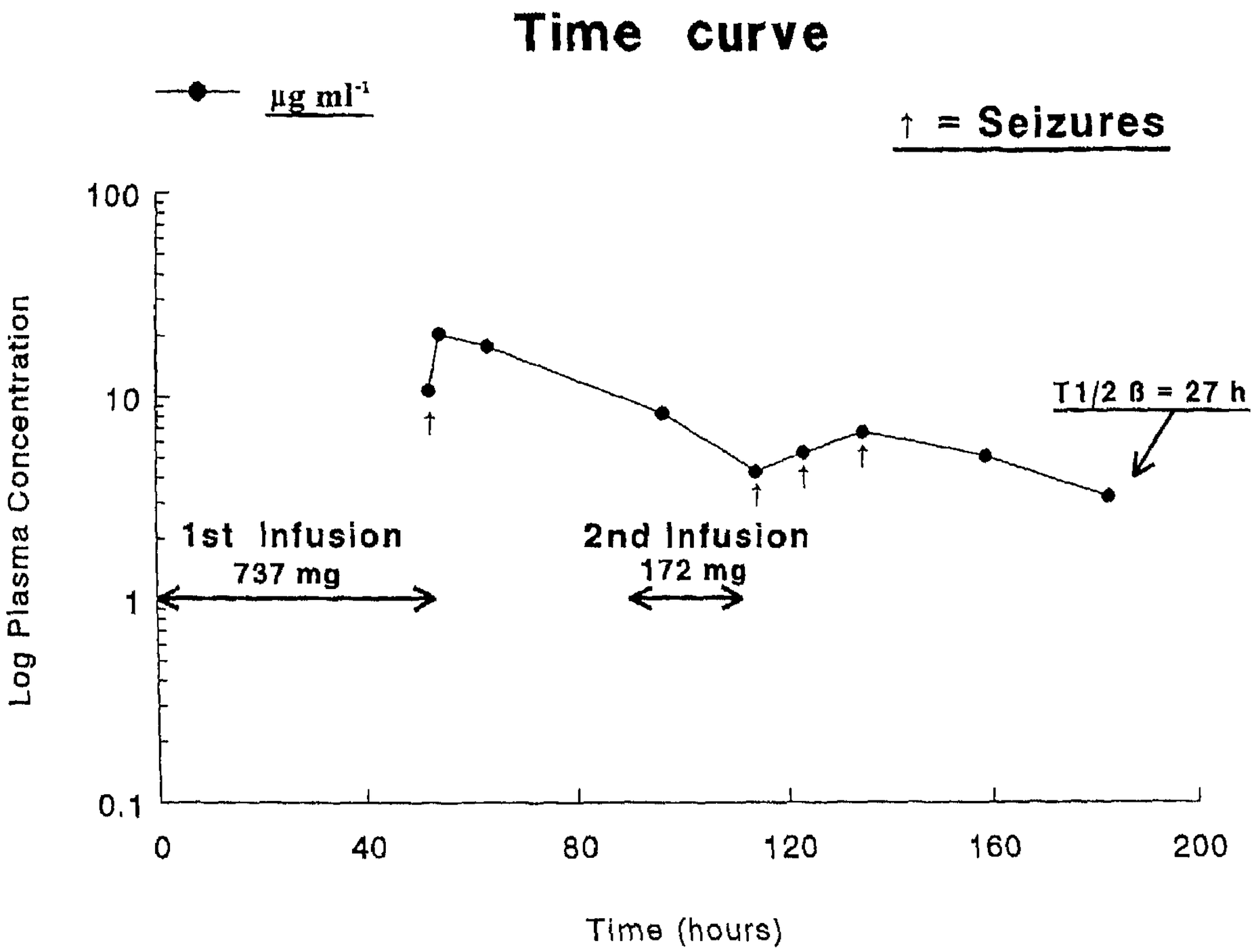

Fig. 1 Bupivacaine plasma concentration.

calculated clearance is therefore overestimated. Because of the highly varying plasma concentration and the re-entering drug dose, it is nearly impossible to properly calculate the clearance.

When the continuous infusion in our patient was stopped the second time, the total bupivacaine concentration was 4.3 µg/mL, and the free bupivacaine concentration was 0.80 µg/mL. The clinical presentation was a generalized tonic clonic convulsion. The patient had two more convulsions, corresponding with total bupivacaine levels of 5.3 µg/mL and 6.7 µg/mL and free bupivacaine levels of 1.12 µg/mL and 1.21 µg/mL. When the patient had a total plasma level of 8.3 µg/mL (at t = 97 hours) with a free bupivacaine level of 0.80 µg/mL, there were no convulsions.

Discussion

Continuous infusion of local anesthetics through the epidural route has gained popularity for the treatment of intractable cancer pain when opioids alone do not give sufficient pain relief.[1] Bupivacaine is the local anesthetic chosen because of its longer duration of action and greater sensory versus motor block.[7] A potential problem with continuous epidural infusion of a local anesthetic agent is accumulation, which may lead to systemic toxic effects.[6,8]

Following rapid bupivacaine infusion, the majority of reported central nervous symptoms occurred between plasma concentrations of 2 and 4 µg/mL (total bupivacaine)[6,8] and 0.24 µg/mL (free bupivacaine).[9] There is evidence that the toxic effects are likely to be more closely related to free unbound plasma concentration than total blood or plasma concentration.[1,4,8] Current understanding of local anesthetic toxicity is limited to experience with single-dose techniques associated with operative or obstetric analgesia, case reports, and animal studies.[1] Patients receiving infusions of bupivacaine may be at increased risk of developing systemic toxicity because of the high plasma concentration.[4,6,8,10,11] A rapid initial absorption phase is followed by a much slower phase. The initial absorption occurs predominantly by uptake into blood vessels from the dense venous plexus within the epidural space, resulting in a high absorption rate and peak concentration. The late absorption phase is due to slow uptake of bupivacaine in epidural fat. This epidural fat can serve as a depot for local anesthetics, in particular for the more liphophilic agents such as bupivacaine. Continuous infusion of this agent results in a rise of epidural fat

concentration followed by a subsequent slow release and resulting longer half-life.[6]

A study of chronic epidural bupivacaine infusions in a population of advanced cancer patients showed asymptomatic patients with total bupivacaine concentrations of 4–5 μg/mL up to concentrations as high as 10.8 μg/mL (total bupivacaine) and 1.01 μg/mL (free bupivacaine).[1] There was considerable inter- and intraindividual variability in plasma bupivacaine concentrations and bupivacaine clearance.[1] Some patients exhibited relative stability of plasma clearance and plasma bupivacaine concentrations during the monitoring period; in other patients there was an increase in plasma bupivacaine concentrations.[1] The calculated total body clearance in these patients was lower.

It is remarkable that after stopping the continuous epidural infusion in this patient, the total plasma level of bupivacaine still rose from 10.7 μg/mL to 20.3 μg/mL (unfortunately, the free bupivacaine levels of these samples were not determined). A continuous release of bupivacaine from the epidural fat depot after stopping the infusion is unlikely to be the cause. Blood concentrations arise from input of the drug in the epidural space and subsequent redistribution between the plasma compartment and the peripheral compartments.[6,12,13] In the case of bupivacaine, this results in at least three input functions into and out of the central compartment. When drug delivery, namely, the epidural infusion, is stopped, it is difficult to understand how the remaining input functions can result in a blood concentration twice that obtained with the epidural infusion in progress. An alternative explanation for this finding is that bupivacaine was trapped in the stomach and a large amount reentered the circulation after gastric emptying occurred.[14] Previous investigations have shown that weak bases will cross the plasmagastric barrier and become concentrated in acid gastric juice. Weak bases will ionize to a greater degree in an acid medium than in a base or neutral environment.[14] Ionized molecules in the gastric fluid are trapped within the gastric compartment. Bupivacaine is a weak base (pKa 8.1).[15] This mechanism is also prescribed for lidocaine (pKa 7.8) after epidural analgesia for vaginal delivery.[14] There was a significant inverse correlation between gastric pH and gastric lidocaine concentration of the neonate.[14] We suggest that gastric lavage is a beneficial treatment for neonatal lidocaine intoxication in these patients.[14] Whether this is the case after prolonged epidural infusion in cancer patients needs further investigation. Gastric lavage should be considered as a treatment after bupivacaine intoxication.

Bupivacaine in human plasma is bound to two types of sites: a low-affinity, high-capacity site (albumin) and a high-affinity, low-capacity site (alpha acid glycoprotein, AAG).[16] With elevated AAG, which is particularly the case in cancer patients, higher than normal Css for a given Ro are found.[6,13,16,17] Increases in AAG increase protein-binding, lowering the fraction of free drug and thus decreasing the Cl. A decrease in Cl could produce a higher incidence of systemic toxicity.[16] This was not observed in several studies and may be due to increased protein binding of bupivacaine to AAG.[16,17] Also, factors other than free versus total bupivacaine concentrations may exist to explain the relative resistance of cancer patients to bupivacaine toxicity.[1]

The plasma drug concentrations of this patient are difficult to explain. It is well documented that the plasma-bound proportion of local anesthetic is inversely related to the drug's plasma level.[12] The higher the plasma level of anesthetic, the more plasma receptors approach saturation, and the fewer binding sites remain unoccupied.[12] The average protein binding of this patient was 85% (±5%, Table 1), a percentage also found by others.[1] Normally the plasma binding of bupivacaine is 96%.[6,15] Our patient had a normal albumin concentration of 45 g/L, so the lower binding was not caused by decreased protein.[17] The lower plasma binding of bupivacaine in our patient can be explained by the saturation or loss of binding sites or conformational changes.[12]

The patient had seizures at a number of low total bupivacaine concentrations but did not have seizures at other higher concentrations. This can be explained by a rapid rise in bupivacaine level after starting the infusion. The rate of increase in plasma concentration is more important than any exact concentration for developing systemic toxicity symptoms.[6] Plasma concentrations of lidocaine injected into the cervical, thoracic, and lumbar epidural spaces are similar, so it appears that there is no difference in the rate of vascular absorption of lidocaine from different parts of the epidural space. However, there are no studies of plasma concentrations obtained during cervical epidural anesthesia using continuous catheter techniques.[18]

By infusing a combination of bupivacaine-opioid, a lower concentration of bupivacaine can be used, thus reducing the risk of toxicity, without affecting analgesia.[4] Further studies are needed to elucidate the mechanism of altered bupivacaine kinetics during prolonged epidural infusion of bupivacaine in cancer patients.[1,13]

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