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Intrapleural Bupivacaine—A Kinetic and Dynamic Evaluation

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Injection of local anesthetics into the pleural space can relieve ipsilateral surgical incisional pain.[1] Reiestad *et al.*[1] used 20 ml of 0.5% bupivacaine with epinephrine, which provided total pain relief in 78 of 81 patients, with only three requiring additional analgesic drugs. The analgesia from the intrapleural injection lasted an average of 10 h, and there were no complications in their series. In our initial evaluation of this technique, we were not able to obtain adequate pain relief using a volume of 20 ml of bupivacaine, and found that an additional 10 ml was necessary for uniformly successful blocks. The use of this large volume of bupivacaine raised concerns about the potential for toxicity. Since there are only limited data on the absorption of local anesthetic agents administered into the pleural space, we followed the clinical course of patients undergoing cholecystectomy who received intrapleural bupivacaine injections and determined the venous plasma levels following the first injection of bupivacaine.

MATERIALS AND METHODS

Eleven consenting adult patients were enrolled in this study, which was approved by our institutional review board. Epidural catheters were placed through a Touhy needle into the right pleural space at the conclusion of surgery with the patient still anesthetized but breathing spontaneously. For the placement of the catheter, the patient was left in the supine position, the right arm abducted to 90°, and the epidural needle passed over the top of the fifth or sixth rib in the mid-axillary line. The intrapleural space was identified by loss of resistance with a well-lubricated glass syringe. In addition to the loss of resistance sign, respiratory movement of the plunger of the syringe was usually, but not always, noted. A 30-ml dose of 0.5% bupivacaine with 1:100,000 epinephrine was injected through the catheter over a 2-min period. Catheters were re-injected over the next 48 h when the patients requested analgesia. Effectiveness of the block was rated on the following scale: 1 = no pain; 2 = minimal pain on deep breathing; 3 = definite pain but not requiring narcotic analgesia; and 4 = pain requiring narcotic analgesia. The area of sensory block was documented using pin prick, and the time between injections and side effects, if any, were also recorded.

After the induction of general anesthesia, all patients had central venous catheters inserted *via* an anticubital vein. These catheters were used to obtain central venous blood samples prior to bupivacaine injection and at 5, 10, 15, 30, and 45 min, and 1, 2, 4, 6, 8, and 12 h post-injection. Blood sampling was stopped before the 12-h specimen if the patient requested a second injection. Thus, the pharmacokinetic analysis represents data from a single bolus injection. The blood samples were immediately centrifuged and the plasma was harvested and stored at −20° C until analysis. Plasma samples were analyzed for bupivacaine within 2 weeks of collection using a modification of the method described by Weigard.[2] The terminal elimination rate constant (λ), elimination half-life ($t1/2\beta$), systemic clearance (Cl_s), volume of distribution at steady state (V_{ss}), and mean residence time (MRT) were determined. The average concentration ($\bar{c}$) of bupivacaine for each patient was determined as the ratio of the total area under the plasma concentration-time curve and MRT. All results are expressed as means (±SD).

RESULTS

The patient population consisted of seven women and four men ranging in age from 29–49 yr. Table 1 demonstrates the number of injections, time between injections, pain score, and sensory level obtained. As the number of injections increased, the time between injections decreased. Whether this was due to individual variation or to tachyphylaxis is not known. Three patients required parenteral narcotics for non-incisional pain. This was either shoulder pain or visceral pain; in

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TABLE 1. Number and Times of Bupivacaine Injections, Pain Score, and Sensory Level Obtained

Injection	# of Pt Injected	Time from Last Injection (H)	Pain Score*	Sensory Level
1	10	N/A	1.4 ± 0.5	T 5–10
2	9	8.3 ± 2.9	1.5 ± 0.5	T 5–9
3	7	7.8 ± 2.8	1.6 ± 0.5	T 5–10
4	6	6.7 ± 1.4	1.5 ± 0.5	T 5–10
5	6	6.4 ± 3.4	1.3 ± 0.5	T 5–11
6	5	5.4 ± 1.6	1.4 ± 0.5	T 5–10
7	4	6.5 ± 2.3	1.3 ± 0.6	T 5–11
8	2	5 ± 0	1.5 ± 0.7	T 6–10
9	1	4.5	2	T 4–11
10	1	5.1	1	T 6–11

Values are mean ± SD.
* See Materials and Methods for description of pain score.

TABLE 2. Maximum Plasma Bupivacaine Concentration (C_{max}) and Time When These Levels were Measured (T_{max})

Patient	C_{max} (μg/ml)	T_{max} (min)
1	2.42	15
2	2.05	30
3	1.71	15
4	1.58	30
5	2.23	15
6	1.10	30
7	1.86	30
8	3.27	10
9	2.23	15
10	2.25	15
Mean ± SD	2.07 ± 0.58	20.5 ± 8.3

one case, the pain was described as biliary colic. The maximum bupivacaine plasma concentration (C_{max}) and the time of maximum plasma concentration (T_{max}) for ten of the 11 patients are shown in table 2. Maximum individual bupivacaine plasma concentrations were reached between 10 and 30 min, and ranged from 1.1–3.3 μg/ml. The 11th patient, whose plasma concentrations were not included in the analysis, had 5 ml of straw-colored pleural fluid aspirated through the Touhy needle at the time of catheter placement. Since no further fluid could be obtained with aspiration and manipulation of the catheter, the decision was made to inject the bupivacaine. Within 1 min of the injection, although still under general anesthesia, he developed seizure activities noted in the head and neck region. Although tachycardia was noted seconds before the onset of seizures, no cardiovascular depression developed; however, awakening was markedly prolonged. This patient's maximum plasma bupivacaine level was 4.9 μg/ml at 5 min following injection. Since this was the first sample drawn following injection, higher plasma levels could have occurred prior to this time.

In seven patients, enough blood samples were obtained to perform a kinetic analysis. The other patients requested re-injection before we could obtain the samples necessary for analysis of the elimination phase of the initial injection. Figure 1 shows the serum concentration of bupivacaine *versus* time. The other pharmacokinetic values obtained were: the terminal elimination rate constant (λ) 0.2 ± 0.04 h^{-1}, the elimination half-life (t 1/2 β) 3.5 ± 0.93 h, systemic clearance (Cl_s) 0.42 ± 0.17 l/h/kg, volume of distribution at steady state (V_{ss}) 1.94 ± 0.37 l/kg, and the mean residence time (MRT) 4.86 ± 1.5 h.

DISCUSSION

Our data indicate that bupivacaine with epinephrine is absorbed from the pleural space at a rate similar to other areas of the body. Moore *et al.*[3,4] demonstrated maximum systemic levels of bupivacaine with epinephrine to occur between 15 and 30 min after epidural injection, 10–20 min after intercostal injections, and 30–35 min post-supraclavicular brachial plexus block. In the only other study in which blood levels were determined following intrapleural bupivacaine, Reiestad *et al.*[5] determined arterial blood levels of bupivacaine obtained following 20-ml injections of a 0.25%, 0.375%, and 0.5% solution containing an unspecified amount of epinephrine. The maximum levels were reached at their 20-min sample. The maximum arterial level reached for 0.5% bupivacaine was 1.18 μg/ml. We cannot directly compare our results to Reistad *et al.'s*, since we measured venous levels and injected a volume of 30 ml. The plasma level of bupivacaine associated with central nervous system toxicity is generally above 4 μg/ml.[6] However, seizure activity has been reported at levels of 2.3 μg/ml[7] and 3.0 μg/ml.[8] Our mean maximum concentration of 2.07 ± 0.58 μg/ml was below these levels, but, in one patient who did not have seizure activity, plasma levels reached 3.27 μg/ml. Our patient who did exhibit seizure activity was well above these levels, with a maximum concentration measured as 4.9 μg/ml.

Reistad *et al.'s*[1] catheter placement was more posterior than we described. Their patients were turned to

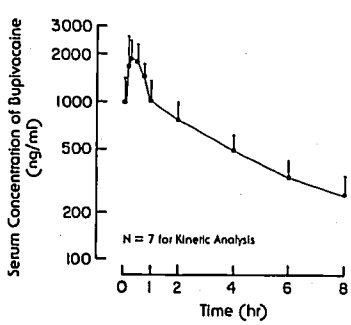

FIG. 1. Mean concentration ± SD of bupivacaine *versus* time following a single intrapleural dose of 30 ml of 0.05% bupivacaine with 1:100,000 epinephrine.

the lateral position with the unoperated side down. The eighth intercostal space was used between 8–10 cm from the vertebral column, and the needle was introduced under the rib in a medial direction. This placement may have required a smaller volume of injection to obtain a satisfactory block. We chose the supine position to avoid the extra movement to the lateral position in a lightly anesthetized patient. We also chose to pass the needle over the top of the rib to avoid laceration of an intercostal artery or vein.

Reiestad *et al.*[1] suggested that fibrosis of the pleural is a relative contraindication of this technique because of difficulty in identifying the intrapleural space using a loss of resistance method. They also consider blood or pleural fluid to be a contraindication because of the dilutional effect they may have on the local anesthetic. In our series, the patient who seized had what appeared to be a very small collection of pleural fluid. The injection was made because no further fluid could be obtained, and we felt there could be no dilutional effect. Since we achieved such high blood levels in a short period of time, we assume the pleura was highly inflamed, and thus allowed rapid absorption. The pleural fluid may have been in a loculation, and, thus, our total volume could have been injected into a very small space. Since this patient had a history of pneumonia which was treated and had resolved 4 weeks preoperatively, we feel that another contraindication to this technique is any recent thoracic infection that might result in an inflamed surface and allow rapid absorption of the local anesthetic. Furthermore, since we noted a tachycardia prior to seizure activities, we feel that heart rate could be used as a marker for a test dose of local anesthetic with epinephrine. Since this patient, we have been giving 5 ml of bupivacaine with 1:100,000 epinephrine and waiting at least 2 min, while monitoring the ECG for heart rate changes before further injection. Another potential cause of this seizure activity would be intravascular injection; however, we did aspirate the catheter before injection, and no blood was retrieved. Reiestad *et al.*'s[5] recent presentation demonstrated effective blocks with 0.25 and 0.375% concentrations of bupivacaine. However, in their series, only 17 of 22 patients had complete relief. Two patients receiving the lower concentrations (0.25 and 0.375%) had unsatisfactory relief at 30 min, and required re-injection. The duration of action was less with these concentrations of bupivacaine.

In addition to systemic toxicity, other potential complications would include pneumothorax. There have been no reports of pneumothorax to date. With an intrapleural catheter in place, the diagnosis would be made easily if air were aspirated.

Intrapleural blocks with bupivacaine provided substantial pain relief in ten of 11 patients. Central venous blood levels were highest at 20.5 ± 8.3 min following injection, with an average maximum concentration of 2.07 ± 0.58 μg/ml. Based on our experience, we feel recent pulmonary infection may be a contraindication to this technique.

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