Convulsive Arterial Plasma Levels of Bupivacaine and the Response to Diazepam Therapy

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To date, no specific data have been obtained in man to confirm or refute the following conclusions: first, arterial plasma levels of bupivacaine of more than 4 μg/ml are necessary to produce a generalized systemic toxic reaction in man; second, administration of diazepam, 0.25 mg/kg, im, 60 min prior to injection of a local anesthetic protects against systemic toxic reactions. Finally, diazepam, 0.1 mg/kg, iv, will abort such convulsions. The first proposition is based on subconvulsive doses of local anesthetic drugs in man and convulsive doses in dogs. The latter two derive from monkey data extrapolated to man.

The following two cases give insight into the arterial plasma levels of bupivacaine that result in convulsions, as well as whether diazepam prevents or aborts convulsions.

REPORT OF TWO CASES

Patient 1. A 41-year-old woman, height 165 cm, weight 57 kg, with a proven inoperable pheochromocytoma with satellite tumors was scheduled for removal of a protruding nucleus pulposus between the fifth lumbar vertebra and the sacrum. No other disease was evident on the basis of history and physical examination. Blood pressure was 130/90 torr, pulse rate 96/min, respiratory rate 12/min. Roentgenograms of the chest and the electrocardiogram were normal.

At 6:30 A.M., morphine sulfate, 8 mg, and atropine sulfate, 0.4 mg, were administered im, with oral administration of 10 mg diazepam (0.18 mg/kg).

At 7:20 A.M., an intravenous infusion of 1,000 ml of lactated Ringer’s solution with 5 per cent dextrose was started in the right hand. Since the patient had a pheochromocytoma, the left radial artery was cannulated in order to monitor blood pressure precisely.

At 7:38 A.M., a 19-gauge needle was introduced into the epidural space at the second lumbar interspace. Aspiration for blood and cerebrospinal fluid was negative.

At 7:40 A.M., 15 ml 0.75 per cent bupivacaine (113 mg) without epinephrine were injected. At the completion of the injection, aspiration for blood or spinal fluid was negative, the needle was removed, and the patient was immediately turned supine. Within a minute, the patient convulsed. Oxygen was given immediately by bag and mask, and diazepam, 15 mg, iv (0.26 mg/kg) was given within 30 sec. After three episodes of convulsive convulsions, convulsions ceased and respirations returned. A sample of arterial blood was drawn at 7:44 A.M. (table 1). The patient was returned to the recovery unit for observation, with a blood pressure of 118/70 torr, pulse rate 108/min, respiratory rate 12/min, and no cardiac irregularity. She regained consciousness at 8:30 A.M. At 8:33 A.M., another arterial blood sample was drawn (table 1). Since no area of analgesia could be detected by Allis forceps pinch and the reaction had occurred within a minute, it was concluded that the local anesthetic solution had been injected intravascularly.

By 11:00 A.M., the patient had regained complete consciousness. She was oriented as to date and place, and her physical status was comparable to her preanesthetic status.

At 11:30 A.M., the patient was returned to the induction room. With her consent, the epidural block was to be repeated. At 11:35 A.M., a 3-ml control sample of arterial blood was drawn, and 5 mg diazepam (0.09 mg/kg) were administered iv (table 1). A 19-gauge needle was inserted into the epidural space, and aspiration produced no blood or cerebrospinal fluid. A 3-ml test dose of 0.75 per cent (23 mg) bupivacaine without epinephrine was administered. After a 2-min wait, there was no evidence of spinal analgesia or systemic toxicity. At 11:43 A.M. and 45 sec, 15 ml 0.75 per cent bupivacaine (113 mg) without epinephrine were injected. As the final milliliter was injected at 11:44 A.M., the patient complained of dizziness, the needle was withdrawn, and she was turned supine. At 11:44 A.M. and 30 sec, she started to convulse, and oxygen was administered by bag and mask. During the convulsion, a sample of arterial blood was drawn, and 7.5 mg diazepam (0.13 mg/kg) were injected iv. The patient had only one convulsive episode. Three additional samples of arterial blood were drawn for analysis (table 1). She regained consciousness at 12:00 noon. At 12:15 A.M., no area of analgesia could be delineated with Allis forceps pinch. General anesthesia was administered for the operation, with no adverse effect during the operation or postoperatively.

Exploration of the epidural space from the second lumbar interspace to the sacrum revealed nothing other than the diagnosed disc at the fifth lumbar interspace. No evidence of bleeding into the epidural space from puncture of a blood vessel(s) was found.
Table 1. Plasma Concentrations of 0.75 Per Cent Bupivacaine during Convulsions, Patient 1

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Time of Completion of Injection</th>
<th>Time of Onset of Convulsions</th>
<th>Time of Sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>First intravascular injection</td>
<td>112.5 mg</td>
<td>7:40 A.M.</td>
<td>7:41 A.M.</td>
</tr>
<tr>
<td>Second intravascular injection</td>
<td>Control</td>
<td>135 mg</td>
<td>11:44 A.M.</td>
</tr>
</tbody>
</table>

* All samples were analyzed in duplicate.

Patient 2. A 65-year-old woman, height 165 cm, weight 55 kg, who had chronic obstructive respiratory disease and thyroiditis was scheduled for nephroureterectomy. No other disease was present. The blood pressure was 120/70 torr, pulse rate 86/min. The history, physical examination, roentgenogram of the chest, and electrocardiogram revealed no other abnormality.

At 7:30 A.M. morphine sulfate, 12 mg, and atropine, 0.4 mg, were administered intravenously.

At 8:25 A.M., an i.v. infusion of 1,000 ml of lactated Ringer's solution with 5 per cent dextrose was started. At 8:45 A.M., the patient requested additional sedation during the preparation for insertion of plastic tubing into the epidural space, and 10 mg diazepam (0.18 mg/kg) were given i.v. When the diazepam did not provide the desired sedation within 10 min, 60 mg thiopental (1.1 mg/kg) were given i.v. In approximately 3 min, sedation was adequate—that is, the patient was drowsy and answered questions slowly and somewhat unclearly. After insertion of the plastic tubing, the patient was placed supine on the operating table. Aspiration for blood and cerebrospinal fluid was negative. At 9:10 A.M., 15 ml 0.75 per cent bupivacaine (113 mg) were injected. Within 60 sec, the patient convulsed. Oxygen was administered. After four convulsions, which occurred within the next minute, 15 mg diazepam (0.27 mg/kg) were given i.v. The convulsions ceased. Half an hour later, the patient regained consciousness. She had no detectable residual anesthesia. General anesthesia was administered for the operation, with no adverse effect intra- or postoperatively.

Conclusions

While specific conclusions cannot be based on the evidence of two cases, certain assumptions seem valid:

A plasma bupivacaine concentration of 5.1 μg/ml causes convulsions. In the first case, an arterial plasma concentration of 5.1–5.4 μg/ml following an i.v. bolus of bupivacaine resulted in convulsions. The convulsions ceased when the arterial plasma bupivacaine concentration was 3.5–3.6 μg/ml. In previous studies, arterial plasma levels of 4.0 μg/ml or less of bupivacaine resulting from absorption after epidural, brachial plexus, bilateral intercostal nerve, or sciatic and femoral nerve blocks did not result in convulsions. Therefore, the prediction that the arterial plasma level of bupivacaine must be more than 4.0 μg/ml before convulsions result appears likely to be accurate.

The prophylactic use of diazepam did not prevent convulsions. In the first case, 10 mg diazepam (0.18 mg/kg), p.o. prior to the first convulsions and 5 mg (0.09 mg/kg), i.v. 9 min prior to the second convulsive episode did not prevent convulsions. Also, in the second case, 10 mg diazepam (0.18 mg/kg), i.v. 15 min prior to injection of the local anesthetic did not prevent convulsions. Perhaps these doses, which are similar to those that were effective in monkeys, were inadequate to prevent systemic toxic reactions in man, because they were too small, the times of administration were not as precise, or both.

Should diazepam routinely be used prophylactically to prevent convulsions? Our overall incidence of convulsions in patients following epidural, caudal, or peripheral nerve block from i.v. injections—that is, convulsions within 1 min and no anesthesia—is one in 850 patients (0.12 per cent). The incidence resulting from absorption—that is, convulsions within 2–5 min and satisfactory anesthesia—is one in 5,540 (0.018 per cent). Lund and co-workers report an even lower incidence of one in 1,105 patients (0.09 per cent) from i.v. injections, and none from absorption. Therefore, if the only reason for giving diazepam preoperatively is to prevent a systemic toxic reaction from local anesthetic drugs, we conclude that patients did not need it, because the occurrence of such a reaction is infrequent and the effectiveness of diazepam for this purpose in man has yet to be proven.

Large doses of diazepam may abort convulsions. When a convulsion starts, usually all available therapeutic means to terminate it are employed—that is, a "shotgun" approach is used. Seldom is adequate time allowed to elapse for one agent (e.g., oxygen) to be effective before another drug (e.g., diazepam) is given. As a result, no-one knows which of the therapeutic...
modalities used in these two cases stopped the convulsions—that is, artificial respiration with oxygen by bag and mask, or diazepam. If diazepam did stop the convulsions, the definitive dose in man has not as yet been determined, and could be larger than that needed to stop convulsions in monkeys.

In these two cases, the doses of diazepam administered iv during the convulsions, which may have been the factor in aborting the convulsions, were larger than those used in monkeys, namely: 1) 0.26 mg/kg; 2) 0.13 mg; 3) 0.27 mg/kg. Perhaps the dose of 0.13 mg/kg, which was significantly smaller than the others, was effective because of the previously administered diazepam—that is, from 6:30 A.M. to 11:35 A.M. the patient received diazepam, 10 mg, po, as well as a total of 20 mg iv (0.35 mg/kg).

Systemic toxic reactions cannot be avoided, but sequelae can. These systemic toxic reactions, resulting from inadvertent iv administration of bolus doses of bupivacaine, as well as those reported to have occurred with other local anesthetic drugs, were not averted by any or all of the following: 1) premedication with diazepam; 2) a dose of the local anesthetic drug less than that recommended by the package insert—that is, 113 mg as compared with 175 mg; 3) negative aspiration tests; 4) a test dose of 3 ml of the local anesthetic solution without epinephrine, 1:200,000. Therefore, to avoid complications from a systemic toxic reaction, the user of the local anesthetic drug must immediately recognize the signs and symptoms of such a reaction, and treat it promptly and effectively.

Appreciation is extended to Astra Laboratories for analysis of the arterial blood samples.

REFERENCES


An Inexpensive Device for Analyzing and Monitoring the Electroencephalogram

ROBERT A. FLEMING, M.S.,* AND N. TY SMITH, M.D.†

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