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Research on local anesthetic neurotoxicity using intrathecal and epidural rat models

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Serious neurologic complications rarely occur after neuraxial blockade. However, reports of cauda equina syndrome after continuous spinal anesthesia, published in 1991 [1], generated concern regarding the potential neurotoxicity of local anesthetics used clinically. Cauda equina syndrome results from injury to the sacral nerve roots and is characterized by varying degrees of bladder and bowel dysfunction, perineal sensory loss, and lower extremity motor weakness. Reviews of such cases and results of studies using anatomic models [2,3] have suggested that the combination of maldistribution and a relatively high dose of local anesthetic may result in toxic exposure of neural tissue.

To identify the factors that contribute to local anesthetic injury, and to pursue investigations of the mechanisms underlying this injury, we have developed in vivo rat models, in which local anesthetic can be continuously administered intrathecally or epidurally [4–6]. To facilitate restricted distribution, catheters are placed with their tips among the nerve roots of the cauda equina [4] or very close to the caudal end of the epidural space [6]. Because local anesthetic solutions rarely induce neurologic injury in clinical practice, the observation of neurotoxic effects requires higher doses of these agents. Thus, a high concentration of local anesthetic is used, and/or continuous infusion is done in our models. Figure 1 shows a typical protocol for our studies, in which functional and histological findings have been obtained. Neurologic function was examined with the tail-flick test and the paw-pressure test. Histological examination of the nerve roots and spinal cord was performed using light and electron microscopy.

Experiments using our in vivo models have produced results that can answer some important questions, one of which is whether local anesthetic neurotoxicity is dose-dependent. We continuously administered 5% lidocaine, with or without glucose, for 30 min, 1 h, 2 h, or 4 h in our rat model [7]. The results of the tail-flick test, performed 4 days after the infusion, showed that rats given lidocaine for longer periods, regardless of glucose, were more likely to incur deficits.

Permanent neurologic injury, including cauda equina syndrome, has been reported to be associated with lidocaine in many cases. Results of experiments where we administered bupivacaine and lidocaine intrathecally as equipotent solutions have proven that bupivacaine is less neurotoxic than lidocaine, suggesting that neurotoxicity differs among local anesthetics [8].

There is a considerable difference between spinal and epidural anesthesia in the number of reported cases of nerve injury. This fact is probably because the neurotoxicity of epidural and intrathecal local anesthetics is different. Our models permit a comparison of the effects of anesthetics administered intrathecally and epidurally. When intrathecal and epidural lidocaine were administered in rats to produce similar anesthetic effects, persistent functional impairment occurred only after

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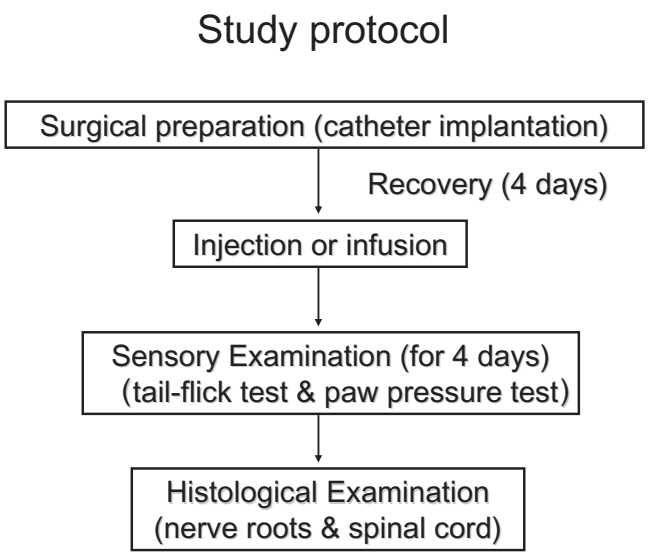

Fig. 1. Study protocol

the intrathecal injection of lidocaine [6]. Histological damage to the nerve roots and the spinal cord was less severe after injection with epidural lidocaine than after intrathecal lidocaine. However, epidural lidocaine is not immune from neurotoxicity. When large doses were continuously administered in rats, the neurotoxic effects of epidural lidocaine, in terms of functional impairment and morphologic damage, were observed in a dose-dependent fashion [9].

Blockade of voltage-gated sodium channels is the prime site of anesthetic action, but this is not the cause of the agents' neurotoxicity. When lidocaine, bupivacaine, and tetrodotoxin, a highly specific sodium-channel blocker, were intrathecally administered at concentrations ten times each respective anesthetic EC50, lidocaine and bupivacaine induced persistent sensory impairment, whereas tetrodotoxin did not, indicating that local anesthetic neurotoxicity does not result from the blockade of sodium channels [10].

In conclusion, our knowledge of local anesthetic toxicity has been remarkably improved in the past 15 years with the use of in vivo animal models that provide a close parallel to problems in the clinical setting. However, much is still unknown, including the etiology of the toxicity. It is believed that in vivo animal models will continue to play an important role in improving our understanding of local anesthetic neurotoxicity.

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