学 位 論 文 の 要 旨

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学 位 論 文 名　Comparative Somatic and Visceral Antinociception and Neurotoxicity of Intrathecal Bupivacaine, Levobupivacaine, and Dextrobupivacaine in Rats

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INTRODUCTION

Bupivacaine, a racemic mixture of S(-) and R(+) enantiomers, has been one of the most widely used local anesthetics because of its long duration of action and less motor impairment. Recently, levobupivacaine, the pure S (-) enantiomer, has been developed for clinical use as an agent that has lower risk of cardiotoxicity than bupivacaine. Because the both enantiomers have different binding affinities to sodium channel, anesthetic effect of levobupivacaine may be different from those racemic bupivacaine.

Bupivacaine has enjoyed its popularity for spinal anesthesia partly because it has rarely been associated with permanent neurologic injury or transient neurologic symptoms. However, it is not known whether the enatiomers of bupivacaine are similar in neurotoxicity.

Accordingly, the current study investigated whether racemic bupivacaine, levobupivacaine, and R (+) enantiomer, dextrobupivacaine differ in somatic and visceral antinociception and sensory impairment, and histologic damage when adiministered intrathecally in rats.

MATERIALS AND METHODS

This study was approved by the Animal Research and Use Committee of Shimane University and was comprised of three experiments. All experiments were conducted in male Sprague-Dawley rats (252-350 g). To reduce the influences of handling on behavioral reactions, all rats were trained in the test situation at least two times before intrathecal catheterization. In experiment 1, rats were implanted with an intrathecal catheter through L3-4 vertebra in the caudal direction and received 15 μl of saline, or 0.125%, 0.25%, 0.5% or 1% bupivacaine, levobupivacaine, or dextrobupivacaine. The tail flick and the colorectal distension tests were performed to assess somatic and visceral antinociceptive effects, respectively, before and for 180 min after the injection. Tail flick and colorectal distension data were converted to the percent maximal possible effect (%MPE), calculated as [(postdrug – baseline)/(cutoff – baseline)] x 100, from which the area under the time-effect curve (AUC) was calculated. The dose-effect relationship for each drug was determined by using AUC values, and the potency ratio was calculated and tested for significance with a computer-based program. Motor function in the lower limbs was also assessed. In experiment 2, rats given 0.25% anesthetic solutions were evaluated with colorectal distension-induced response in blood pressure and heart rate. In experiment 3, rats were randomly divided into four groups to intrathecally receive a 1-hr infusion of saline, or 2.5 % bupivacaine, levobupivacaine, or dextrobupivacaine. Additional rats received either 1.25% bupivacaine or levobupivacaine for 60 min. Four days after infusion, animals were assessed for persistent sensory impairment using the tail flick test and paw pressure test. Then animals were sacrificed, and spinal cords and nerve roots were obtained for histologic analysis. Nerve injury was determined using light microscopy and was calculated as the average score of fascicles present on sections.

RESULTS AND DISCUSSION

In experiment 1, the three drugs produced similar time-course effects and dose-effect

relationship in tail flick latency. In contrast, colorectal distension thresholds and motor paralysis were slightly lower and less apparent, respectively, at some concentrations in rats given levobupivacaine than in those given the other agents. In experiment 2, the response in heart rate was significantly decreased immediately after injection in all of the animals tested. However, colorectal distension induced response in heart rate was less depressed in rats given levobupivacaine than in those given other anesthetics. Because mechanical stimulation of the gut has been demonstrated to produce cardiovascular responses as well as visceromotor responses, heart rate was analyzed to compare the effect of the three drugs. In experiment 3, the three drugs were administered at the same concentration because their dose-effect curves obtained in experiment 1 were almost identical. Four days after infusion, three groups of rats given anesthetic solutions developed similar significant increases in tail flick latency and incurred similar morphologic damage. However, the degree of injury suggested that there might have been a ceiling effect and differences in effects might be present at lower concentrations. Therefore, we conducted the additional study comparing 1.25 % anesthetic solutions. Two groups of rats receiving 1.25% anesthetic solutions were similar in functional impairment and nerve injury scores. Because our previous study showed that bupivacaine is less neurotoxic than lidocaine, levobupivacaine and dextrobupivacaine seem to be similarly less neurotoxic than lidocaine.

CONCLUSION

Intrathecal bupivacaine and its R(+) and S(-) enantiomers produced similar prolongation of tail flick latency and nerve injury scores. Colorectal distension threshold and motor function score of levobupivacain was slightly lower than those of others. The results suggest that intrathecally administered bupivacaine and its enantiomers are similar for somatic antinociception and neurotoxicity. In terms of visceral antinociception and motor paralysis, levobupivacaine is slightly less potent than the others.