Letter to the Editor

In reply to “Is intrathecal lidocaine administration risk-free in rats with neuropathic pain?”

We thank Drs. Umbrain, Smolders, and Poelaert for their interest in our finding that high doses of intrathecal (i.t.) lidocaine have long-lasting therapeutic effects on established hyperalgesia and allodynia (Tian et al., 2009).

In concurrence with Dr. Umbrain et al., the possible neurotoxicity of i.t. lidocaine was also an issue that we considered and discussed in our report. We assessed this based on neurofunctional and morphologic findings, including walking ability, sensory threshold (in another set of normal rats), and histopathologic evaluations. We completely agree with Dr. Umbrain et al. that it would be interesting and informative to explore the local neurotoxic effects in more detail, perhaps including neuronal mitochondrial functions, which will be included in our future studies.

We want to emphasize here that we never intended to imply that i.t. lidocaine therapy for neuropathic pain was risk-free. As mentioned in the paper, severe respiratory depression, hypotension, and neurotoxic effects were all observed in rats after application of i.t. lidocaine, especially with high doses (Tian et al., 2009). Clinical use of this method should be based on very careful assessment of the risk-benefit ratio. We recommended 15 mg/kg i.t. lidocaine based on our findings in CCI rats, the clinical value of which may correspond to a dose in human beings that just reaches the dose range causing total spinal anesthesia. Future studies are required to explore this issue in other neuropathic pain models before extrapolation to clinical practice.

Dr. Umbrain et al. mentioned that in their findings, 400 or 1000 µg i.t. lidocaine injection increased prostaglandin E2 (PGE2) levels in the cerebrospinal fluid (CSF) for 90–120 min, along with a persistent period of mechanical and thermal hyperalgesia in free moving rats. They therefore concluded that i.t. lidocaine induced a temporary state of spinal cord sensitization (Umbrain et al., 2008). One key difference between their study and ours is that they focused on the effects of i.t. lidocaine in normal bodies, while our purpose was to investigate the role of i.t. lidocaine in neuropathic pain states. The effects of a given drug on the same system might be entirely altered in different physiological states. Indeed, Ma et al. previously reported that i.t. lidocaine could down-regulate prostaglandin (PG) systems in the spinal cord following peripheral nerve injury (Ma et al., 2003). Recently, our group found that i.t. lidocaine reduced p38 mitogen-activated protein kinase (MAPK) activation in microglia in the spinal cord of neuropathic rats (Gu et al., 2008). Active p38 MAPK in the microglia is known to play a pivotal role in the spinal release of cytokines, including PGE2 (Ajmone-Cat MA, Nicolini A, Minghetti L. Llong-lasting therapeutic effects on established hyperalgesia and allodynia [Chapman et al., 1998]. Consistent with these mechanistic studies, numerous behavioral studies in animals as well as in clinical patients clearly indicate that lidocaine given intrathecally can indeed reduce neuropathic pain (Yamashiro and Hirano, 1987; Mao and Chen, 2000; Yokoyama et al., 2002; Ma et al., 2003). In Japan, intentional total spinal anesthesia is a pain-relief therapy approved by the Ministry of Health and Welfare (Yokoyama et al., 2002). Taken together, these reports as well as our findings (Gu et al., 2008; Tian et al., 2009) support the hypothesis that i.t. lidocaine is effective in relieving certain types of neuropathic pain, and indicate that the underlying mechanisms are likely to be complicated. But again, this method should only be an option for those patients where the benefits from i.t. lidocaine outweigh the risk of side effects.

We agree with Dr. Umbrain et al. that the effects of i.t. lidocaine on centrally induced cytokines are worth considering. This is an area of research currently under investigation in our lab.

References


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