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Neurotoxicity of local anesthetics; June 1, 2007, Sapporo, Japan

Opening remarks

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Local anesthetic agents are relatively free of side effects, with a 50-fold margin between median blocking and toxic concentrations, implying a safer therapeutic window than that for many other clinically available drugs. However, when these agents are administered in excessive doses or in the incorrect location, such as accidental intravascular or intrathecal injection, systemic or localized toxic reactions may occur. Local neuronal tissue toxic reactions occur rarely when clinically relevant concentrations of local anesthetics are used. The neurotoxicity of local anesthetics has been extensively investigated by groups all over the world. However, the mechanism(s) remain incompletely understood. Several Japanese researchers are particularly active in this area and four of them participated in discussions of this issue in the *Journal of Anesthesia*—sponsored symposium: Neurotoxicity of Local Anesthetics.

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Carl Koller is credited with the first description of the local anesthetic action of cocaine, in 1884 [1], leading to the eventual introduction of local anesthesia worldwide. Five percent hyperbaric lidocaine has been used for millions of spinal anesthetic procedures since its introduction in 1948. Phillips and colleagues [2] prospectively studied the safety of intrathecal lidocaine with 10440 patients from 1961 to 1966, and concluded that lidocaine was safe for spinal anesthesia. However, Rigler and colleagues [3] reported four cases of cauda equina syndrome after continuous spinal anesthesia, in 1991. Transient neurologic symptoms (TNS) were also reported by Schneider et al. [4] in 1993. They found that 4 patients undergoing spinal anesthesia with lithotomy positioning complained of aching and pain in the buttocks and lower extremities postoperatively. Since these reports, several epidemiological studies regarding neurologic deficits after regional anesthesia have been performed, and these raised several possible causes, such as specific local anesthetic toxicity, needle trauma, neural ischemia secondary to sciatic stretching, patient positioning, pooling of local anesthetics, muscle spasm, myofascial trigger points, early mobilization, and irritation

of the dorsal root ganglion [5]. Similarly, neurologic deficits during peripheral nerve block may also occur via intraneural injection resulting from local anesthetic neurotoxicity or mechanical trauma such as direct needle trauma and tourniquet-induced injury. In addition, a vascular mechanism is also known to contribute to nerve injury. This is caused by a prolonged increase in endoneurial pressure exceeding capillary perfusion pressure as a consequence of an injection of local anesthetic into the perineurium, resulting in endoneurial ischemia [6]. When vasoconstrictor agents are added, the ischemia would, theoretically, be worse, with a reduction in regional blood flow [7]. However, as the relative risk for developing TNS after spinal anesthesia with lidocaine compared to other local anesthetics (bupivacaine, prilocaine, procaine, levobupivacaine, and ropivacaine) was 7.16 [8], lidocaine per se would produce TNS (neurotoxicity of lidocaine) but spinal block may not. Therefore, during regional anesthesia it is likely that there is technically unavoidable neurologic damage caused by local anesthetics per se. Johnson and colleagues [9] reported that lidocaine neurotoxicity involved mitochondrial injury, with activation of caspase leading to apoptosis. However, they also found that z-VAD-fmk, a specific caspase inhibitor, delayed but did not prevent neuronal death. Recently, the group of Lirk et al. [10] and Haller et al. [11] have found that a specific and time-dependent activation of the p38 mitogen-activated protein kinase (MAPK) is involved in the neurotoxicity of lidocaine and amitriptyline, most likely followed by the activation of lipooxygenase pathways. In addition, they also suggest that inhibition of p38-MAPK might prevent local anesthetic-induced neurotoxicity [10,11].

We hope that today's discussion will provide a useful exchange and some further insights into the mechanism(s) of local anesthetic neurotoxicity that may lead to the safer use of these useful agents in our clinical practice.

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