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Intrathecal *S*(+)-ketamine in refractory neuropathic cancer pain

Dear Editor,

As intrathecal preservative-free *S*(+)-ketamine proved clinically safe and very effective in our hands as a last resort for the relief of refractory neuropathic pain (Sator-Katzenschlager et al., 2001; Benrath et al., 2005), we read with great interest the Clinical Note on the neuropathological findings in the spinal cord after continuous intrathecal administration of *S*(+)-ketamine (Vranken et al., 2005). Severe histopathological abnormalities in the spinal cord and nerve roots including central chromatolysis, nerve shrinkage, neurophagia, microglial upregulation, and gliosis have been observed after intrathecal infusion of up to 50 mg/day *S*(+)-ketamine for 28 days in a cancer patient. These changes would suggest behavioral or clinical signs of neurotoxicity which, however, were reported to be absent in this patient.

Interestingly, previous reports on neurotoxicity of ketamine showed controversial results. When comparing these reports, the use of different ketamine preparations has to be considered. In most countries, exclusively racemic ketamine formulations (50% *S*(+) and 50% *R*(−)-ketamine) are available either preservative-free or with preservatives such as benzetholium chloride and chlorobutanol. While racemic ketamine with preservatives induced mild spinal cord vacuolation as the predominant histopathological finding (Karpinsky et al., 1997; Stotz et al., 1999), preservative-free racemic ketamine has been shown to be devoid of neurotoxic effects after both single and repeated administration in animals (Brock-Utne et al., 1982; Malinovsky et al., 1993; Errando et al., 1999). No animal data exist on potential pathomorphological effects of the pure *S*(+)-ketamine enantiomer. Using preservative-free *S*(+)-ketamine (22 mg/day), clonidine (540 μg/day), and morphine (58 mg/day) for 30 days in a patient with pelvic chondrosarcoma, we performed post-mortem histological examination of the upper cervical spinal cord and the brainstem. The patient died due to sepsis and cardio-respiratory failure after his tumor resection. In contrast to Vranken et al. we found no specific signs of neurotoxicity. Only moderate reactive gliosis in the trigeminal nuclei with activated microglia was found which is frequently encountered in sepsis and severe illness. The discrepancy between our case and the report by Vranken et al. may be explained by the high doses of additional drugs used in the latter such as bupivacaine (95 mg/day), the site of histological examination, and the confounding effect of repeated radiation which itself may also induce neuronal chromatolysis.

We agree with the authors that the lack of safety data on neurotoxicity does limit the neuroaxial administration of *S*(+)-ketamine. However, we have to acknowledge that intrathecal *S*(+)-ketamine is a potent option in the treatment of chronic severe neuropathic pain in cancer patients refractory to conventional therapeutic strategies (Benrath et al., 2005) and should, therefore, be used as a last resort when other options have failed.

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Response to Kozek et al.

We are pleased that Dr. Kozek and his colleagues take interest in our work, and we appreciate the opportunity to respond to each of the insightful remarks posed in Dr. Kozek's letter.

The search for alternative analgesic drugs has drawn renewed attention to ketamine (and the *S*(+)-isomer) for neuraxial use in patients with postoperative pain and to relieve chronic neuropathic pain. The antinociceptive effect of ketamine on somatic and visceral pain has been described in animals and humans. However, despite considerable clinical experience, there is still controversy in the literature (human and animal) as to the safety of ketamine and *S*(+)-ketamine for either intrathecal or epidural administration (Eisenach and Yaksh, 2003). In our patient, severe histological abnormalities in the spinal cord were observed following a combination of morphine, bupivacaine, clonidine, and *S*(+)-ketamine (Vranken et al., 2005). Although morphine, clonidine, or bupivacaine may be responsible for the observed histopathological changes, comparable studies using clinically relevant concentrations and doses of each drug (animal and human) did not provoke such neurohistopathological changes (Sjöberg et al., 1992; Wagemans et al., 1997). Despite the changes in the spinal cord, there were no signs of behavioral or clinical signs of neurotoxicity in our patient. Although deterioration of behavior may indicate neurotoxicity, the converse is not invariably true. Thus, clinical observations alone provide insufficient evidence for proving neurotoxicity, emphasizing the importance of assessing spinal histopathology to evaluate the neurotoxicity of spinal drugs (Yaksh and Allen, 2004).

Because co-administration of *S*(+)-ketamine proved effective in relieving neuropathic pain, studies on neurotoxicity are required before this technique can be recommended or discouraged for clinical practice especially in acute and nonmalignant pain syndromes (Sator-Katzenschlager et al., 2001; Vranken et al., 2004; Benrath et al., 2005). In this view, we recently submitted an animal study to assess the safety and justifiability of this compound for neuraxial administration.

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