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In Reply—Because chronic inflammatory reactions occurred in patients receiving morphine with and without preservatives, our study does not indicate that morphine preparations with preservatives are more neurotoxic than the preservative-free preparations. Thus, no proof emerges from our study that the intrathecal administration of sodium metabisulfite and ethylenediaminetetraacetic acid (EDTA) should be harmful in the doses we used. There was no significant intrathecal inflammation in 13 cases in which patients were given continuous infusion 3.1–1,050 mg of sodium metabisulfite (0.05–0.2 mg/ml) and 0.33–105 mg EDTA (0.005–0.02 mg/ml) for 4–274 days.

With respect to the lesions described by Wang et al. as pachymeningeal evidence of EDTA neurotoxicity when intrathecally administered in rats, we reviewed the literature for the dose and mode of administration (single dose or continuous infusion) of the preservative used in the study and noted that no such study exists. In their previous reports, Wang et al. mentioned that they injected 0.1 ml of 0.1% EDTA (0.1 mg/ml) subarachnoidally in rabbits, i.e., a concentration 5–20 times higher than the concentrations used in our study in humans. Furthermore, in rats, Wang et al. administered five hourly doses of 0.05 ml subarachnoid Na2EDTA 0.3 mm (≈0.1 mg/ml), 0.75 mm (≈0.3 mg/ml), 1.5 mm (0.6 mg/ml), and 3 mm (≈1 mg/ml), on different days. Once again, the concentrations of EDTA used in this study were 5–200 times higher than those we used in our rats. After the injections, the rats developed tetanic contractions at concentrations of 1.5–3.0 mm (≈0.6–1 mg/ml). Wang et al. concluded that “the effect of Na2EDTA appears to be concentration-dependent.” We fully agree with their conclusion.

In clinical conditions, epidural injections of morphine solutions containing sodium edetate (as much as 20–27 mg sodium edetate per day) did not result in clinical complications that could be attributed to the EDTA-containing opioid during 15,023 treatment days and 57,087 injections.

Regarding combined bisulfite + EDTA neurotoxicity: in a recent study, we analyzed the incidence of clinical signs potentially indicating preservative-related neurotoxicity: seizures, spinal clonus, alodinia, paresthesia–hyperesthesias, paresis–paralysis, guilt and sphincter disturbances (fees incontinence and urinary retention), meningeal reaction, and pustulosis in 125 patients treated for 3–352 (median 39) days with preservative-containing (sodium edetate and sodium metabisulfite) morphine solutions. The concentrations of the EDTA in this study varied from 0.0001–0.075 (median 0.01) mg/ml and the daily doses from 0.01 to 1.92 (median 0.1) mg. The concentrations of sodium metabisulfite in the study ranged from 0.001 to 0.75 mg/ml (median 0.1 mg/ml) and the daily doses from 0.1 to 19.2 (median 1) mg. Thus, the sodium metabisulfite concentrations were 5–80 times less than those used by Wang and associates in rabbit experiments; 5–80 times less than the concentration of sodium bisulfite showing a degree of neurotoxicity when intrathecally administered in rabbits and 15–240 times less than those causing irreversible hindlimb deficits in 60% of the rats when intrathecally administered through implanted subarachnoid catheters. Furthermore, we compared the clinical results (as well as the neuropathologic micrographs) from this series with those from another series of 23 patients treated with preservative-free morphine. We did not find any differences between the series, either in clinical or (for autopsied patients) neuropathologic terms.

We stress that we do not conclude, as Wang et al. say, the “low concentrations of sodium metabisulfite and EDTA do not cause neurotoxicity.” Neither do we attribute the pathologic lesions to tumor invasion, radiation therapy, and treatment with neurotoxic agents. Rather, we stated, “Thus, in the low dose range of our study, no influence of dose or exposure time of metabisulfite on neuropathology was possible to detect against the background of other confounding factors, especially tumor infiltration of the meninges and nervous structures.”

Finally, the last sentence of our paper reads: “With the presence of such major disease-related pathology, the separate role of the different treatment-related factors (e.g., catheter material and intrathecally administered drugs and their concentrations, proportions, volumes, osmolarities, and treatment duration) in the occurrence of the neuropathologic findings reported in this study could not be identified.”

In conclusion, we agree with Wang et al.: the preservatives (EDTA and bisulfites) are indeed neurotoxic, but as with all other neurotoxic substances, the neurotoxicity of the above-mentioned preservatives is concentration-, dose-, contact time- and possibly species-related. However, we have been unable to find any clinical and neuropathologic proof of neurotoxicity of EDTA and sodium metabisulfite when these preservatives were administered intrathecally in patients with terminal, “intractable” cancer pain, in the doses and concentrations used in our studies. Furthermore, even if a certain degree of neurotoxicity might have taken a neuropathologic expression, it has been impossible to identify and separate it from the other (above-named) confounding factors. Wang and associates are correct: one cannot extrapolate the histopathologic findings from healthy rabbits and rats to severely ill cancer patients with intraspinal metastases (accounting for their “intractable” pain) and sequelae of chemotherapy and radiation therapy. When the neurotoxicity found in experiments on healthy animals has no clinical significance in the advanced cancer patient, it is justified (in our opinion) to use morphine containing EDTA and bisulfite preservatives when society and the patient lack the economic ability to pay for the substantially more expensive preservative-free morphine. Thus, we and many others, including some in the United States are following the practice described in our paper.

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Emergence Delirium Following Oral Ketamine

To the Editor—We would like to report a severe emergence reaction associated with the use of an oral ketamine premedication as described by Gunstein et al.1

An otherwise healthy 2.5-yr-old girl, weighing 12.4 kg, was scheduled for bilateral myringotomy and insertion of tubes. Her father, a dentist, contacted the anesthesia department the day before surgery to request that his daughter receive preanesthetic medication for the procedure. This was to be her fourth ear surgery, and she had always become extremely agitated prior to the previous surgeries.

On arrival in the day surgery unit, the child was apprehensive yet moderately cooperative with an examination of her airway, heart, and lungs. Preanesthetic medication seemed unnecessary, and inhalation induction with her father holding her was planned. When it was time for surgery, however, she cried loudly, clung to her mother, and would not go with her father. A few minutes later 6 mg/kg (75 mg) of ketamine was given to her in 4 ml of ginger ale. She drank it completely but commented unfavorably on its taste. Twelve minutes later she was easily carried by her father into the operating room. She cried briefly when the mask was applied but was asleep within 90 s.

The procedure was uneventful, and the patient arrived in the postanesthesia care unit crying, 38 min after having ingested the oral ketamine. The child spent the next hour in her mother’s arms. She stared blankly into space, screamed wildly, and then settled down. This cycle was repeated every 2 min or less. One hour and 18 min after arrival in the postanesthesia care unit, she fell asleep. She awoke 67 min later, calm, smiling, and seemingly happy, and was discharged.

Hannahlah and Patel2 used ketamine 2 mg/kg intramuscularly as a premedication in 20 children for bilateral insertion of tympanotomy tubes with complete success and without emergence delirium. These children arrived in the postanesthesia care unit an average of 19 min after their premedication. Gunstein et al.1 also used ketamine 6 mg/kg orally, with complete success and without untoward emergence phenomena. However, these surgeries were considerably longer, and the patients arrived in the postanesthesia care unit 90 min after the premedication. Our patient was in the recovery room 38 min after her oral premedication.

The combination of a large dose of ketamine and a short surgical procedure may predispose to the occurrence of emergence delirium. This reaction was severe, prolonged, and not at all welcome in a busy, open day surgery recovery room setting. We suggest that oral ketamine not be used for procedures expected to last less than 1 h. For shorter procedures, intramuscular ketamine or agents without the described side effect should be considered.

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