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Are the Preservatives Sodium Bisulfite and Ethylene Diaminetetraacetate Free from Neurotoxic Involvement?

To the Editor:—In a recent paper, Sjöberg *et al.*[1] concluded from findings from 15 *post mortem* examinations that low concentrations of sodium metabisulfite and ethylene diaminetetraacetate (EDTA) do not cause neurotoxicity, dismissing without substantiating evidence significant pathologic findings. In addition, one patient developed paraplegia and urinary retention 158 days after the start of the intrathecal treatment. The authors called this "an expected consequence of large daily doses (7–10 mg/h) of intrathecal bupivacaine given to cope with severe neurogenic pains" and attribute the pathologic lesions to tumor invasion, radiation therapy, and treatment with neurotoxic agents. Without a control study to substantiate their conclusions, it seems inappropriate to make such claims. Premature exoneration of bisulfite and EDTA from causing neurotoxicity may cause medical professionals to disregard the potential neurotoxicity of the preservatives and thus jeopardize patients' safety.

We have observed nearly all of the focal lesions described by Sjöberg *et al.* in an animal model after EDTA[2–4] administration in the absence of tumor invasion, radiation, or treatment with other neurotoxic agents. Irreversible hindlimb paralysis in rabbits, after cumulative doses of intrathecal bisulfite, has also been reported.[5]

Sjöberg *et al.*[1] tended to ignore pathologic findings when clinical signs of neurologic deficits are absent. The animals in our EDTA (but not bisulfite) study presented positive pathologic findings yet did not exhibit clinical evidence of chronic neurologic impairment before the time of autopsy. It is true that we are extrapolating our observations in animals to humans, but we believe that significant pathologic findings should not be disregarded.

Sjöberg *et al.*[1] hinted that low concentrations of the preservative are safe, but this may not be true, especially in the case of bisulfite. Sulfite is broken down by sulfite oxidase.[6] In patients with sulfite oxidase deficiency, even a low concentration of bisulfite may be pathogenic.

A host of toxic effects have been reported after enteral and parenteral EDTA administration.[7–15] Patients are especially at risk for hypocalcemia as a result of parathyroid hormone deficiency, impaired calcitriol synthesis, hypomagnesemia, and diseases of kidney and liver.[16] Vitamin D is synthesized in the skin or absorbed by the gut, 25-hydroxylated in the liver, and then 1-hydroxylated in the kidneys to its most active form, calcitriol. Therefore, diseases of the kidney and liver may impair calcium homeostasis; in patients with such ailments, even a low concentration of EDTA may be unsafe.

We do not assume that preservatives are responsible for all the lesions reported by Sjöberg *et al.*,[1] but at the same time, we can not rule out EDTA or bisulfite as the cause of neurotoxicity in some of the cases.

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In Reply:—Because chronic inflammatory reactions occurred in patients receiving morphine with and without preservatives, our study[1] 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 ethylene diaminetetraacetate (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 3.3–1,050 mg of sodium metabisulfite (0.05–0.20 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 pathoanatomic evidence of EDTA neurotoxicity when intrathecally administered in rats, the concentrations, doses, and mode of administration (single dose? continuous infusion?) of the preservative used in the study are not specified. 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,[2] *i.e.* a concentration 5–20 times higher than the concentrations used in our study in humans. Furthermore, in rats,[3] Wang *et al.* administered five hourly doses of 0.05 ml subarachnoid Na_2 EDTA 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 patients. 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 Na_2 EDTA 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.[4]

Regarding combined bisulfite + EDTA neurotoxicity: in a recent study,[5] we analyzed the incidence of clinical signs potentially indicating preservative-related neurotoxicity: seizures, spinal clonus, allodynia, paresthesia–hyperesthesia, paresis–paralysis, gait and sphincter disturbances (feces incontinence and urinary retention), meningeal reaction, and pruritus 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 ≈2.5–80 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;[6] and 15–240 times less than those causing irreversible hindlimb deficits in 60% of the rats when intrathecally administered through implanted subarachnoid catheters.[7] 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) in 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."[1]

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[8] are following the practice described in our paper.[1]

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