

## CORRESPONDENCE

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## Intrathecal Baclofen in Tetanus: Alternative Methods of Administration

*To the Editor:*—Saissy *et al.*<sup>1</sup> reported the efficacy of flumazenil in counteracting the central nervous system depression induced by intrathecal administration of baclofen. As in a previous report from this group,<sup>2</sup> large boluses of baclofen were given intrathecally to control the rigidity and spasms of tetanus, favoring this method of drug administration over continuous infusion in view of "simplicity, safety, and low cost." Although recognizing that these benefits support the use of intermittent intrathecal administration of baclofen in certain economic and demographic settings, we urge caution in using this method of intrathecal baclofen administration because of the increased risk of overdose.

Experience with the use of continuous intrathecal infusion of baclofen in the treatment of intractable spasticity due to multiple sclerosis, spastic paraplegia, and traumatic spinal cord injury established the safety of this method of drug administration. Baclofen shows significant variability in its pharmacokinetics following intrathecal injection, with an elimination half-life between 0.9 and 5 h reported in a study on four patients.<sup>3</sup> After lumbar intrathecal administration, Penn and Kroin<sup>4</sup> reported that the lumbar to cervical baclofen ratio was 4.1:1, and therefore, the concentration of baclofen that reached the brain was not large. After bolus administration, however, higher concentrations would be expected centrally, with resultant increased toxicity, as demonstrated by Saissy *et al.*,<sup>1</sup> and as other authors report following inadvertent or intentional bolus therapy.<sup>5</sup>

Current recommendations for intrathecal administration of a baclofen test dose in patients with causes of spasticity other than tetanus are doses of 25-50 µg, although we have not encountered problems using test doses of 50 µg followed by 75 or 100 µg. This is to avoid

precipitating an overdose in patients who may be unduly sensitive to the drug. In tetanus, the sensitivity to intrathecal administration of baclofen is decreased, because larger bolus doses are well tolerated. However, because most medical centers in developed countries have the facilities available for continuous intrathecal administration through a lumbar intrathecal catheter connected to an external infusion pump, it is difficult to justify the increased risk associated with a large bolus.

Of reported cases<sup>6</sup> that used intrathecal baclofen infusion in the management of tetanus, a dosage range of 600-2,000 µg/day by continuous intrathecal infusion was effective. Müller *et al.*<sup>6</sup> also used large boluses of up to 1,000 µg baclofen given intrathecally in tetanus. However, an initial bolus of 200 µg baclofen, with consideration of the intrathecal half-life of baclofen when increasing the infusion rate or giving additional boluses, should allow for safer use of this therapy.

Practical considerations are the risk of infection with an external infusion device and the cost of an implantable infusion device. A compromise would be the use of a subcutaneous port to allow regular (every 6 h) intrathecal injection, which carries a smaller risk of infection (than the external infusion device), significantly less cost (than the implantable infusion device), and through the use of more frequent and smaller doses of baclofen, less risk of overdose (than the intermittent lumbar puncture technique).

The experience of Saissy *et al.*<sup>1</sup> in treating tetanus with baclofen given intrathecally is far greater than ours; however, like Müller *et al.*,<sup>6</sup> we believe that, when facilities are available for continuous infusion, this may be preferable. Intermittent intrathecal injection through a subcutaneous port also should be considered as an ac-

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ceptable compromise of both techniques. We would like to emphasize that the larger test doses used in patients with tetanus should not be administered to patients with other causes of spasticity.

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## The Safety of Sevoflurane in Humans: I

*To the Editor:*—In a recent editorial,<sup>1</sup> Mazze asks whether sevoflurane is safe for humans, emphasizing the toxicity of  $\text{CF}_2 = \text{C}(\text{CF}_3)\text{OCH}_2\text{F}$  (compound A) reported in our paper.<sup>2</sup> However, his editorial may be misleading and we describe here in greater detail our findings on the toxicity of compound A.

First, Mazze describes the toxicity of compound A as follows: "nonlethal signs of toxicity, which occurred at all doses, included ear and tail flush, decreased locomotion, decreased respiratory rate, cyanosis, tremor, ptosis, and piloerection." This assessment differs from ours, perhaps because some methodologic aspects of our study were not described clearly. Ear and tail flush was seen in all groups, including the 100%  $\text{O}_2$  control group. The flush comes from oxygenation. This change disappeared within 10 min in the recovery cage and was not a sign of toxicity. The decreased locomotion, decreased respiratory rate, and ptosis were seen equally during inhalation of isoflurane\* and sevoflurane.† These changes disappeared within 20 min in the recovery cage. Tremor and piloerection were seen in a few rats before death, and cyanosis was seen before death of the rats. We should emphasize that the ear and tail flush, decreased locomotion, decreased respiratory rate, and ptosis were not signs of

toxicity attributed to compound A. However, the changes in tremor and piloerection were evidence of toxicity.

Second, Mazze also mentions that, "in rats, compound A was lethal at 340-350 ppm, and significant signs of toxicity were seen at levels as low as 110 ppm"; using the references of daily drinking water,<sup>3,4</sup> he states that, "while the circumstances of exposure are vastly different, factors of 2-8 are very low and, in my opinion, should not be ignored." We do not understand why he employed the level of 110 ppm as toxic. Compound A at neither 110 nor 250 ppm was associated with toxicity in our study. The degree of toxicity is to be expressed as  $\text{LC}_{50}$  or  $\text{LD}_{50}$ , and our studies were designed to determine them. This was the reason why the detailed description concerning signs and symptoms of rats was omitted in our paper.<sup>2</sup> Furthermore, findings obtained following chronic oral administration and acute inhalation are vastly different. For example, the  $\text{LC}_{50}$  and  $\text{LD}_{50}$  of inhalational anesthetics are close to the minimum alveolar concentration. Thus, new criteria for acute toxicity on inhalational chemicals are required.

Third, from our study,<sup>2</sup> the  $\text{LC}_{50}$  of compound A in rats was 1,050-1,090 ppm (1 h) and 400-420 ppm (3 h), and a peak concentration of 15 ppm was detected in human low-flow anesthetic circuit with soda lime.<sup>5,6</sup> Renal tubular necrosis (RTN) was found in the groups of more than 700 ppm (1 h) and 290 ppm (3 h).

Kodama‡ reported a maximum level (ML) of 4.5 ppm of 2-bromo-2-chloro-1,1-difluoro ethylene (BCDFE), a byproduct of halothane with soda lime, in an experimental closed circuit, and Sharp *et al.*<sup>7</sup> reported a ML of 5 ppm in a human low-flow anesthetic circuit with soda lime, but that test was not with baralyme. Raventós and Lemon<sup>8</sup> reported that  $\text{LC}_{50}$  of BCDFE (1 h) in mice was 250 ppm and observed RTN at more than 60 ppm (1 h). These values can be compared as follows:

\* Fukushima T, Tomizawa N, Hayakawa K, Yamada H, Watanabe Y, Funahashi N, Nakazawa M: Acute toxicity studies of isoflurane in mice and rats. *The Clinical Report* 21:3031-3036, 1987.

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