Pharmacological Effects of a New Inhaled Anesthetic in Fischer-344 Rats

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Background/Introduction: There are numerous characteristics of the ideal inhalational anesthetic, including potency, low blood:gas solubility, inflammability, and resistance to degradation and metabolism, among others. We have identified a novel compound that holds promise as an inhalational anesthetic. This compound is a member of the class of 1,3-dioxolanes, heterocyclic acetals which have a five-member ring structure, with two oxygens in the ring at the 1,3 positions. We studied *trans*-2,4,5-trifluoro-2-trifluoromethyl-1,3-dioxolane (EXP-GA-23A), a halogenated dioxolane that has saline:gas and oil:gas solubility characteristics similar to isoflurane. We determined the potency of EXP-GA-23A to produce immobility in response to noxious stimulation in rats, and its effects on blood chemistries and hematology (to determine any organ toxicity and fluoride levels to determine extent of metabolism). For comparison, we also studied a group of rats anesthetized with sevoflurane.

Methods: Fisher-344 rats (N=6) were anesthetized in acrylic cylinders using a calibrated vaporizer that delivered EXP-GA-23A. Anesthetic requirements were determined by adjusting the EXP-GA-23A concentration (measured using gas chromatography), and applying a tail clamp to elicit gross, purposeful movement. The EXP-GA-23A

concentration was adjusted in an up-and-down method to find the concentrations that permitted, and prevented, movement in response to the clamp; the minimum alveolar concentration (MAC) was the median concentration, as calculated using logistic regression. After 120 minutes of anesthetic exposure, a laparotomy was performed and the rat exsanguinated. Blood chemistry, hematology and fluoride levels were determined. Another group of rats (N=5) were anesthetized with sevoflurane for comparative purposes.

Results: Anesthetic requirements for EXP-GA-23A were 2.1 ± 0.1% (mean, SEM); sevoflurane requirements were 3.4 ± 0.1%. There were no clinically meaningful differences in blood chemistries or hematology values between the two groups. The fluoride concentrations in four of six EXP-GA-23A rats were below the limit of detection (0.05 µg/ml), while two rats had values of 0.051 and 0.057 µg/ml, respectively. The fluoride concentration was 0.24 ± 0.02 µg/ml in the sevoflurane-anesthetized rats. Spontaneous motor activity was not observed in any of the rats. Overall, the rats appeared to tolerate the two-hour exposure to EXP-GA-23A and sevoflurane.

Conclusions: EXP-GA-23A appeared to be well tolerated with no obvious organ toxicity after two-hour exposures. The fluoride concentrations were less than those found with sevoflurane, suggesting minimal metabolism. EXP-GA-23A shows potential as a new inhalational anesthetic.