Metoprolol for the Prevention of Emergence Delirium after Sevoflurane Anesthesia in Children

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Introduction: Despite the well-known advantages that have made sevoflurane the agent of choice in pediatric anesthesia, it is associated with a disturbing increase (up to 80%) in emergence delirium (ED) (1). In the clinical presentation of this poorly understood phenomenon, younger patients are usually agitated, non-purposefully restless, combative, and prone to crying and moaning; while older children are more often fearful, paranoid, and disoriented (2). Strong evidence suggests a link between the neurotransmitter norepinephrine (NE) and anxiety and fear (3). Sevoflurane can increase NE levels in the rat brain (4) and in the blood of human volunteers receiving concentrations routinely used in children (5), though the underlying mechanism remains poorly understood. Anxiety neurosis and stress have been successfully treated using β-adrenergic blockers (6), which probably modulate NE metabolism in the brain.

Case Report: A mature and self-composed 46 kg 12-year-old Caucasian female with a history of hydronephrosis was scheduled for cystoscopy and left ureteral stent placement. Over the course of the previous year, she had had four sevoflurane-based anesthesia interventions, and according to her mother, after each she had cried in consolably, hid under blankets, thrashed about, yelled, and even struck out at recovery room staff. On this occasion, the patient underwent slow mask induction of anesthesia with oxygen (\text{O}_2), nitrous oxide (\text{N}_2\text{O}) and sevoflurane 2% to 8%. Mask ventilation was without incident, but as she fell unconscious, motor excitability was apparent and her heart rate increased from 85 beats/min (BPM) to sinus tachycardia in the 180s. A 20G intravenous catheter was placed, 2 µg/kg of Fentanyl and 0.1mg/kg of vecuronium were administered, and the patient was intubated with a 6.0 cuffed endotracheal tube (ETT). Although anesthesia was maintained with a 1.5 MAC sevoflurane, 50% \text{O}_2/\text{N}_2\text{O} mixture, the patient remained tachycardic with BPM in the 140s. She was administered 0.1 mg/kg of Lopressor (Metoprolol tartrate) intravenously over 10 min, resulting in normalization of her heart rate to BPM in the 80s and a decrease on the Bispectral Index System (BIS) reading from the 60s to the 40s, allowing the reduction of sevoflurane to 0.5 MAC for the remainder of the one-hour operation. Upon emergence and extubation, the patient opened her eyes and was immediately cognizant of her surroundings, remaining calm and cooperative. In the PACU, she did not cry or express fear or confusion, to the surprise of her mother, who had never seen her daughter wake up so calmly from anesthesia. Discharged from the PACU after 25 minutes, the patient was allowed to go home shortly thereafter.

Discussion: Previous studies in animal models have shown that the anxious or fearful behaviors triggered by stressful events are accompanied by a marked increase in NE in the hypothalamus, amygdala and locus coeruleus (LC) of the brain. Both the behavior and the NE levels can be significantly attenuated by benzodiazepines, opiates and clonidine, medications that decrease LC/NE activity (3). This same therapeutic approach has been used with varying degrees of success for the prevention and treatment of ED in children (1). Electrical stimulation of the LC in sleeping monkeys is known to increase levels of NE in the brain, CSF, and plasma, waking the animals and causing them to exhibit anxious behaviors, including head and body turning, eye scanning, scratching, escape struggling, and hair and skin pulling (7). Interestingly, some of these behaviors mimic those observed in infants and pre-school children with severe ED.
Metoprolol, a selective $\beta_1$-adrenergic receptor antagonist, crosses the blood-brain barrier, achieving concentrations up to 78% of the simultaneous plasma concentration. $\beta_1$-adrenergic receptor antagonists block the effects of NE by preventing both the activation of adenylate cyclase by the stimulatory G protein and the subsequent formation of the second messenger, cyclic adenosine monophosphate (cAMP). Although we were aware of the beneficial effects of the $\alpha_2$-agonist for the prevention of ED, we could not use it in this instance as the medication was not a part of the pharmacy formulary at our institution.

We hypothesize that sevoflurane induces an exaggerated response of the brain/NE system, one which could be prevented by modulating the central release of NE ($\alpha_2$-agonist) or by blocking its actions on target centers in the brain ($\beta_1$-blockers). An elucidation of this system and its physiological implications would greatly improve our understanding of the effect of inhalation agents on brain functions. Studies are needed which evaluate both the potential benefits and possible side effects of $\beta$-blockers in the prevention and treatment of emergence distress in younger patients.

References:
4. Ogasawara H., Masui, 1992
5. Hall J.E. et al., Anesthesia, 2000