

# Isoflurane therapy for status asthmaticus in children: A case series and protocol

Derek S. Wheeler, MD; Christopher R. Clapp, MD; Michael L. Ponaman, MD; Heather McEachren, BSN, PNP; W. Bradley Poss, MD

**Objective:** To describe the use of inhaled isoflurane by using a standardized protocol in the treatment of respiratory failure secondary to status asthmaticus in a series of pediatric patients.

**Design:** Case series.

**Setting:** Pediatric intensive care unit of a tertiary care military medical facility.

**Patients:** Six pediatric patients ranging in age from 14 months to 15 yrs who were treated with isoflurane in our pediatric intensive care unit for status asthmaticus from 1995 to 1998.

**Intervention:** Inhaled isoflurane therapy was initiated by using the treatment protocol after the patients had failed conventional medical management in the treatment of their asthma.

**Measurements and Main Results:** All patients tolerated isoflurane therapy well by using our standardized protocol in conjunction with careful hemodynamic monitoring and support. The ad-

ministration of inhaled isoflurane resulted in measurable improvements in the subject patients, as evidenced by statistically significant decreases in  $Paco_2$  and peak inspiratory pressures, as well as a significant increase in pH. All six patients were successfully extubated and were discharged from the hospital without apparent sequelae.

**Conclusions:** We conclude isoflurane may be a safe, effective treatment modality in the management of status asthmaticus refractory to aggressive medical therapy, although further study is warranted. We emphasize this mode of therapy should be instituted only after traditional treatment modalities have failed and appropriate intensive care support is available. (*Pediatr Crit Care Med* 2000; 1:55-59)

**Key Words:** asthma; inhalational anesthetics; isoflurane

Asthma is the most common chronic disease affecting children and remains one of the most common reasons children require hospitalization. Despite improvements in outpatient management, the frequency of pediatric asthma-related hospitalizations and mortality has continued to rise in certain subsets of the population (1-3). Subsequently, there has been great interest in the identification and development of new treatment modalities for the increasing number of children who develop respiratory failure secondary to status asthmaticus. Recent studies have examined several different

treatment methods, including the use of helium-oxygen gas mixtures, magnesium sulfate, and permissive hypercapnia (4, 5). Although these treatments appear to be promising, they by no means represent a panacea for the management of status asthmaticus, and the search for better treatments continues.

Inhalational anesthetic agents were used in the treatment of status asthmaticus refractory to traditional medical therapy as early as 1939 (6). However, their use has been limited outside the operating room setting by concerns over toxicity, as well as by the technical expertise and specialized equipment required for their use. Isoflurane, a halogenated ether with relatively few side effects, has been used successfully in the treatment of status asthmaticus (7). The experience with inhalational isoflurane in children, however, is limited. We retrospectively studied the use of isoflurane in six pediatric patients by using a standard protocol for treatment of respiratory failure secondary to status asthmaticus. The patients, ranging in age from 14 months to 15 yrs, were treated in our pediatric intensive care unit (PICU) from 1995 to 1998. Five patients were intubated and on maximal

medical therapy before the institution of inhaled isoflurane treatment. Shortly after returning from the operating room, one patient was placed on isoflurane after an episode of severe bronchospasm during induction for a surgical procedure.

## CASE REPORTS

**Patient 1.** A 13-yr-old, 80-kg female with previous, multiple ward admissions for asthma presented to the emergency department (ED) in acute distress after awakening with symptoms of severe shortness of breath. Her outpatient regimen consisted of theophylline and daily use of an albuterol metered dose inhaler. In addition, she had been prescribed both nedocromil and flunisolide metered dose inhalers, although she had not been compliant with these medications. She was admitted to the PICU after multiple treatments with aerosolized albuterol and ipratropium, subcutaneous epinephrine and terbutaline, and intravenous methylprednisolone and magnesium sulfate. Despite aggressive treatment, she developed respiratory failure and was subsequently intubated. On transfer to the PICU, she was sedated and paralyzed with ketamine,

---

From the Department of Pediatrics, Naval Medical Center, San Diego, CA.

Sponsored, in part, by NSHSBETHINST 6000.41A.

The views expressed in this article do not reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

Address requests for reprints to: Clinical Investigation Department, Code AVA, Medical Editing Division, Naval Medical Center San Diego, 34800 Bob Wilson Drive, Suite 5, San Diego, CA 92134-1005. E-mail: wbposs@nmcscd.med.navy.mil

Copyright © 2000 by the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies

midazolam, and vecuronium. Further treatment included intermittent aerosolized albuterol and ipratropium, a continuous aminophylline infusion, intravenous methylprednisolone, and empirical antibiotic coverage for a right lower lobe infiltrate. Because of her worsening condition, a continuous terbutaline infusion starting at 0.5  $\mu\text{g}/\text{kg}/\text{min}$  and increasing to 1  $\mu\text{g}/\text{kg}/\text{min}$  was added. Boluses of magnesium sulfate were administered to maintain serum magnesium levels  $>1.23$  mmol/L. She was placed on volume-control ventilation with an initial tidal volume of 600 mL, positive end-expiratory pressure of 6 cm  $\text{H}_2\text{O}$ , and rate of 25 breaths/min. Her peak inspiratory pressure (PIP) slowly decreased to 40–45 cm  $\text{H}_2\text{O}$  with a tidal volume of 600–700 mL, but on hospital day (HD) 3 her PIP increased to 55 cm  $\text{H}_2\text{O}$  with a tidal volume of 600 mL. Arterial blood gases showed worsening respiratory acidosis with a pH 7.27 and a  $\text{Paco}_2$  of 77 torr (Table 1). Inhaled isoflurane therapy was subsequently instituted at a concentration of 0.2% and slowly increased to 1.5%. While receiving isoflurane, she required intermittent fluid boluses for a decreased urine output, but she did not develop any evidence of hypotension. Her PIPs decreased to 25–35 cm  $\text{H}_2\text{O}$ , her respiratory acidosis resolved (Table 1), and she was gradually weaned from isoflurane on HD 4. The total duration of isoflurane therapy was 24 hrs. Extubation was unsuccessfully attempted on HD 6; she required mechanical ventilatory support for an additional 72 hrs before successful extubation and transference to the ward on HD 11.

**Patient 2.** A 14-yr-old, 50-kg male with a history of moderate asthma was intubated in the ED for respiratory failure secondary to status asthmaticus. He had presented with 2 days of upper respiratory infection symptoms, and he noted increased wheezing and dyspnea on the day of admission. His maintenance medications were nedocromil, beclomethasone, and albuterol metered dose inhalers. Before transfer to the PICU, he had been treated with continuous aerosolized albuterol and ipratropium, intravenous methylprednisolone, a continuous terbutaline infusion, and sedation. He was placed on volume-controlled ventilation, with resultant PIPs of 40–50 cm  $\text{H}_2\text{O}$  on a tidal volume of 400 mL. On arrival at our PICU, terbutaline was continued at 0.8  $\mu\text{g}/\text{kg}/\text{min}$ . Shortly after admission he had a sudden decompensation associated with worsening bronchospasm. He

Table 1. Summary of isoflurane experience with six pediatric patients

Preisoflurane				
Patient	Age/Sex	pH	$\text{Paco}_2$ (torr)	PIP (cm $\text{H}_2\text{O}$ )
1	13 yrs/F	7.27	77	62
2	14 yrs/M	6.96	96	60
3	10 yrs/M	6.99	110	60
4	15 yrs/M	7.05	85	64
5	15 months/F	7.07	72	$>30$ (anesthesia bag)
6	14 months/F	Unavailable	$>60^a$	60–65
Postisoflurane				
Patient	Elapsed Time	pH	$\text{Paco}_2$ (torr)	PIP (cm $\text{H}_2\text{O}$ )
1	10 mins	7.45	45	45
2	30 mins	7.30	44	45
3	30 mins	7.30	50	35
4	40 mins	7.08	65	45
5	78 mins	7.18	59	22
6	12 mins	7.28	48	35

PIP, peak inspiratory pressure; To convert torr to kPa, multiply value by 0.1333.

<sup>a</sup>End-tidal  $\text{CO}_2$  monitoring.

subsequently developed bilateral pneumothoraces associated with the onset of ventricular tachycardia. He was successfully cardioverted and bilateral chest tubes were placed after needle thoracotomy. In addition, he developed moderate hypotension, which responded to both fluid resuscitation and pressor support with an epinephrine drip of 0.1  $\mu\text{g}/\text{kg}/\text{min}$ . He developed significant respiratory acidosis (Table 1) over the next 4 hrs with no evidence of recurrent pneumothoraces. Isoflurane at an inhaled concentration of 1.5% was administered to treat his bronchospasm. His respiratory acidosis improved significantly with a reduction in his PIP (Table 1). Treatment with intravenous ketamine for sedation and bronchodilation was instituted; intravenous terbutaline was decreased to 0.5  $\mu\text{g}/\text{kg}/\text{min}$  and corticosteroid therapy was continued at 1 mg/kg every 6 hrs methylprednisolone. He was weaned off epinephrine in the next 36 hrs and was weaned off isoflurane on HD 4, with extubation performed later that day. The duration of isoflurane therapy was approximately 96 hrs.

**Patient 3.** A 10-yr-old, 30-kg male with a known history of asthma was admitted to the PICU after a 1-day history of upper respiratory infection symptoms and worsening respiratory distress. His outpatient regimen was albuterol, triamcinolone, and nedocromil. He was admitted to the PICU after multiple treatments with aerosolized albuterol, ipratropium, and intravenous corticosteroids. An initial arterial blood gas demonstrated a pH

of 7.22,  $\text{Paco}_2$  of 55 torr, and a  $\text{Pao}_2$  of 120 torr on 10 L/min supplemental oxygen via a nonbreathing face mask. He was placed on continuous aerosolized albuterol, methylprednisolone 1 mg/kg intravenously every 6 hrs, and intravenous terbutaline at an infusion rate of 4  $\mu\text{g}/\text{kg}/\text{min}$  after a 10  $\mu\text{g}/\text{kg}$  bolus. Over 1 hr, 1 g iv of magnesium sulfate was administered with no further improvement. The child became markedly fatigued and difficult to arouse, and a rapid sequence intubation was performed. Initial peak pressures were as high as 60 cm  $\text{H}_2\text{O}$  with tidal volumes of 8 mL/kg. The patient's condition continued to deteriorate despite addition of chemical paralysis and a continuous ketamine infusion. A repeat arterial blood gas showed a pH of 6.99,  $\text{Paco}_2$  of 110 torr, and a  $\text{Pao}_2$  of 130 torr. Inhalational isoflurane therapy was administered at a concentration of 2%. Treatment with all other medications except terbutaline and methylprednisolone was discontinued. The patient developed moderate hypotension, which responded to a decrease in the isoflurane to 1% and a dopamine infusion of 5  $\mu\text{g}/\text{kg}/\text{min}$ . After 30 mins of inhalational isoflurane, the PIP decreased to 30–35 cm  $\text{H}_2\text{O}$  and the respiratory acidosis improved. Ventilatory support was gradually weaned over the next 24 hrs, and the patient was extubated 48 hrs after admission. The duration of isoflurane therapy was ~44 hrs. The patient was discharged to home ~48 hrs after extubation.

**Patient 4.** The 14-yr-old, 50-kg male patient described as patient 2 presented

again with respiratory failure 5 months after his initial hospitalization. Before intubation at an outside ED, he received continuous albuterol and ipratropium nebulizer therapy and intravenous methylprednisolone. He was intubated and a right chest tube was placed for a suspected pneumothorax. In transport, he was treated with continuous albuterol, magnesium sulfate bolus, and a single theophylline bolus. On arrival to the PICU, his initial venous blood gas measurement was notable for a pH of 7.15 and a  $\text{Paco}_2$  of 61 torr. A terbutaline infusion was administered after a 10- $\mu\text{g}/\text{kg}$  bolus and was subsequently increased from 2  $\mu\text{g}/\text{kg}/\text{min}$  to 10  $\mu\text{g}/\text{kg}/\text{min}$  with further clinical deterioration. Sedation was maintained with continuous infusions of midazolam and fentanyl. He developed a significant respiratory acidosis (Table 1) on volume-controlled ventilatory support with PIP at 60 cm  $\text{H}_2\text{O}$  and a tidal volume of 400 mL. Isoflurane was initiated at 1% with a rapid decrease in his PIP to 45 cm  $\text{H}_2\text{O}$  and an improvement in his respiratory acidosis (Table 1). He required fluid resuscitation and a dopamine infusion of 15  $\mu\text{g}/\text{kg}/\text{min}$  and epinephrine infusion of 0.1  $\mu\text{g}/\text{kg}/\text{min}$  to maintain adequate blood pressure until the isoflurane was weaned <1%. During treatment with isoflurane, therapy was continued with methylprednisolone at 1 mg/kg every 6 hrs, continuous terbutaline infusion at 2  $\mu\text{g}/\text{kg}/\text{min}$ , and magnesium sulfate boluses to keep serum magnesium levels >1.23 mmol/L. Isoflurane was discontinued at ~40 hrs and he was extubated the next day without incident.

**Patient 5.** A 14-month-old, 9.9-kg female with a history of Apert's syndrome and mild intermittent asthma was admitted for an elective craniofacial reconstruction. Her home medications were glycopyrolate for secretion management and intermittent aerosolized albuterol. Her past medical history was remarkable for a tracheostomy placement at 2 months of life and several previous respiratory admissions; however, she was reportedly free from viral symptoms at the time of operation. She was noted to become acutely bronchospastic ~4 hrs into surgery with a balanced fentanyl and isoflurane anesthesia technique, and she underwent an emergent bronchoscopy with removal of mucus plugs. Surgery was canceled, isoflurane was discontinued, and she was admitted to the PICU.

On arrival at the PICU, she required PIPs of 45 cm  $\text{H}_2\text{O}$  to maintain adequate tidal volumes of 8–10 mL/kg. An arterial blood gas measurement on 100% oxygen was obtained, showing a pH of 7.18, a  $\text{Paco}_2$  of 85 torr, a  $\text{PaO}_2$  of 326 torr, and a base deficit of -7.2. A continuous terbutaline infusion was administered at 0.4  $\mu\text{g}/\text{kg}/\text{min}$  after a 10  $\mu\text{g}/\text{kg}$  loading dose, which was quickly increased to 1  $\mu\text{g}/\text{kg}/\text{min}$  because of clinical deterioration. In addition, she was placed on continuous aerosolized albuterol and ipratropium and intravenous methylprednisolone. After ~1 hr of therapy, inhaled isoflurane was initiated at 1% secondary to persistently high PIPs of 45–50 cm  $\text{H}_2\text{O}$  and worsening clinical status. The isoflurane concentration was increased to 1.5% before a clinical response was noted with a decrease in her PIP to 30 cm  $\text{H}_2\text{O}$  and a drop in the  $\text{Paco}_2$  to 50 torr (Table 1). The elapsed time from initiation of therapy to clinical response was ~1 hr. She required a 20 mL/kg fluid bolus secondary to hypotension after the increase in isoflurane concentration, and she ultimately required a dopamine infusion to maintain an adequate blood pressure until the isoflurane was decreased <1%. She remained on inhalational therapy for ~20 hrs and on HD 3 was transferred to the ward.

**Patient 6.** A 14-month-old, 12.9-kg female was admitted to the PICU after presenting to the ED in respiratory distress. She had been evaluated 2 wks previously by her pediatrician, who had prescribed albuterol and erythromycin for wheezing and breathing difficulty. Her symptoms had improved until the day before admission, when she returned to her pediatrician with increasing cough and fever. She was treated with prednisolone 2 mg/kg/day, albuterol and cefixime for a presumed pneumonia. On presentation to the ED, she was noted to be in respiratory failure with oxygen saturation of 79% on room air. She was emergently intubated and transferred to the PICU.

She was admitted to the PICU and placed on aerosolized albuterol and ipratropium, methylprednisolone 2 mg/kg iv, a terbutaline infusion at 0.4  $\mu\text{g}/\text{kg}/\text{min}$  after a 10  $\mu\text{g}/\text{kg}$  loading dose, and volume-control ventilation. She continued to worsen with PIPs increasing to >60 cm  $\text{H}_2\text{O}$  to maintain adequate tidal volumes (Table 1). Terbutaline was increased to 5  $\mu\text{g}/\text{kg}/\text{min}$  and a ketamine infusion was initiated at 1 mg/kg/hr. She did not improve, and inhaled isoflurane

therapy was initiated at 1%, increasing to 1.5% before a clinical response was obtained, as evidenced by a decrease in her PIP to 35 cm  $\text{H}_2\text{O}$  and a decrease in her end-tidal  $\text{CO}_2$  from 60 to 50 mm Hg. She developed hypotension requiring a dopamine infusion for the first 48 hrs of therapy. While she was on isoflurane, therapy with iv methylprednisolone, ketamine, and terbutaline was continued. To maintain serum magnesium levels >1.23 mmol/L, magnesium sulfate was administered. She was placed on oxacillin at 72 hrs when her tracheal aspirate grew *Staphylococcus aureus*. She remained on inhalational therapy for 160 hrs and was extubated on HD 7 with transfer to the ward on HD 9.

## MEASUREMENTS AND MAIN RESULTS

Our experience with the six patients outlined in Table 1 demonstrates the potentially beneficial effects of isoflurane therapy in severe status asthmaticus. Our standardized protocol for the initiation and administration of isoflurane therapy is outlined in the Appendix. All patients but one were on maximal medical therapy as detailed in the preceding case reports before the initiation of isoflurane treatment. The 15-month-old patient in our series experienced life-threatening bronchospasm during an operative procedure and was admitted to the PICU. Although she developed bronchospasm on isoflurane while in the operating room, her clinical course and subsequent response to the reinstitution of isoflurane were similar to those of the other patients.

Statistical analyses of blood gas values and pre- and post-isoflurane changes in PIP were performed by using the Wilcoxon's rank sign test. This group of patients exhibited a statistically significant increase in pH ( $p = .043$ ), as well as statistically significant decreases in  $\text{Paco}_2$  ( $p = .028$ ) and PIP ( $p = .027$ ).

## DISCUSSION

Status asthmaticus is defined as a condition of progressively worsening bronchospasm unresponsive to appropriate therapy. It is characterized by bronchial muscle spasm, mucosal edema, mucosal inflammation, and mucus plugging of the

**W**e present our experience with the use of inhalational isoflurane in the management of a series of pediatric patients with life-threatening asthma. By using a standardized protocol, we were able to safely use isoflurane with apparently beneficial effects.

airways, often leading to severe hypoxemia and respiratory acidosis. Therapy generally includes the administration of supplemental oxygen, beta-adrenergic agonists, and corticosteroids; however, in selected patients, controlled ventilation may be required for the treatment of impending respiratory failure.

Historically, inhalational anesthetics have been occasionally used in patients with status asthmaticus unresponsive to more traditional therapies. The bronchodilator effects of the inhalational anesthetics are well known. Proposed mechanisms of action include beta-adrenergic receptor stimulation, direct relaxation of bronchial smooth muscle, inhibition of the release of bronchoactive mediators, antagonism of the actions of both histamine and acetylcholine, and depression of vagally mediated airway reflexes (8). Preliminary studies in certain animal models suggest inhalational anesthetics may mediate bronchodilation via an epithelial-dependent mechanism involving either nitric oxide or a prostanoid (9, 10).

Halothane has been used as an effective bronchodilator both in anesthetic practice and in the treatment of patients with status asthmaticus (11–14). The use of halothane has been limited, however, because of concerns over toxicity. Potential adverse effects include myocardial depression, arterial hypotension, and arrhythmias. Furthermore, these adverse side effects may be potentiated by hypoxemia, hypercapnia, and acidosis, as well as certain pharmacologic agents used in the treatment of asthma, notably the

methylxanthine derivatives and beta-adrenergic agonists (14, 15).

The use of isoflurane in the treatment of status asthmaticus offers several advantages over halothane. First, because it is the least fat soluble and has the lowest blood gas solubility coefficient of all the inhalational anesthetics, the depth of anesthesia can be rapidly adjusted and recovery from anesthesia is relatively short. In addition, at concentrations >1.15%, the depth of anesthesia is sufficient so that the use of other sedatives and muscle relaxants is rarely required. Second, isoflurane produces less myocardial depression and is less arrhythmogenic compared with other inhalational anesthetics. Finally, although isoflurane produces dose-dependent hypotension via direct vasodilation, there is a compensatory increase in heart rate so that cardiac output is unchanged. Furthermore, the hypotension produced is usually responsive to volume support (16–18). However, we recommend close monitoring of arterial blood pressure in these patients. Treatment of resultant hypotension should include volume support, pressor support, and gradual decreases in the concentration of the inhalational isoflurane.

The toxic metabolites of both enflurane and halothane have been implicated in both hepatic and renal injury. Isoflurane, on the other hand, undergoes minimal metabolism. Fluoride ions are released after metabolism, and isoflurane anesthesia has been associated with an increased plasma fluoride concentration, although without any effect on renal function (19, 20). The highest fluoride ion concentration documented after isoflurane anesthesia is 36.8  $\mu\text{M}$  (21). Generally, fluoride-induced nephrotoxicity occurs at plasma fluoride levels >50  $\mu\text{M}$ , although subclinical nephrotoxicity may occur at levels as low as 33.6  $\mu\text{M}$  when present for an extended length of time, such as during the management of status asthmaticus (22, 23). In our protocol, we routinely monitored both renal and hepatic function. None of the six patients demonstrated evidence of either renal or hepatic toxicity. We suggest that both renal and hepatic function be monitored closely. Fluoride levels should be obtained in those patients developing evidence of renal or hepatic dysfunction while receiving prolonged isoflurane anesthesia. Further, the concentration of isoflurane should be decreased in those

patients whose fluoride levels approach 30  $\mu\text{M}$ .

In summary, we present our experience with the use of inhalational isoflurane in the management of a series of pediatric patients with life-threatening asthma. By using a standardized protocol, we were able to safely use isoflurane with apparently beneficial effects. Each of the patients demonstrated improvements in pH,  $\text{PaCO}_2$ , and ventilatory pressures, usually within 30 mins of beginning isoflurane therapy. Obviously, because of the limitations of a retrospective case series, it is difficult to formulate any definitive conclusions regarding the efficacy of the use of isoflurane in the management of status asthmaticus. However, based on our experience, as well as that of others (24), we feel this treatment modality warrants further consideration and research.

## REFERENCES

1. Mannino DM, Homa DM, Pertowski CA, et al: Surveillance for asthma: United States, 1960–1995. *Mor Mortal Wkly Rep CDC Surveill Summ* 1998; 47:1–27
2. Asthma mortality and hospitalization among children and young adults: United States, 1980–1993. *JAMA* 1996; 275:1535–1537
3. Goodman DC, Stukel TA, Chang C: Trends in pediatric asthma hospitalization rates: Regional and socioeconomic differences. *Pediatrics* 1998; 101:208–213
4. Jagoda A, Shepherd SM, Spevitz A, et al: Refractory asthma: Part 1, epidemiology, pathophysiology, pharmacologic interventions. *Ann Emerg Med* 1997; 29:262–274
5. Jagoda A, Shepherd SM, Spevitz A, et al: Refractory asthma: Part 2, airway interventions and management. *Ann Emerg Med* 1997; 29:275–281
6. Meyer NE, Schotz S: Relief of intractable bronchial asthma with cyclopropane anesthesia: Report of case. *J Allergy* 1939; 10: 239–240
7. Parnass SM, Feld JM, Chamberlin WH, et al: Status asthmaticus treated with isoflurane and enflurane. *Anesth Analg* 1987; 66: 193–195
8. Hirshman CA, Edelstein G, Peetz S, et al: Mechanism of action of inhalational anesthesia on airways. *Anesthesiology* 1982; 56: 107–111
9. Park KW, Dai HB, Lowenstein E, et al: Isoflurane- and halothane-mediated dilation of distal bronchi in the rat depends on the epithelium. *Anesthesiology* 1997; 86:1078–1087
10. Park KW, Dai HB, Lowenstein E, et al: Epithelial dependence of the bronchodilatory effect of sevoflurane and desflurane in rat distal bronchi. *Anesth Analg* 1998; 86:646–651
11. Gold MI: Anesthesia for the asthmatic patient. *Anesth Analg* 1970; 49:881–888

12. Gold MI, Helrich M: Pulmonary mechanics during general anesthesia: V. status asthmaticus. *Anesthesiology* 1970; 32:422-428
  13. Echeverria M, Gelb AW, Wexler HR, et al: Enflurane and halothane in status asthmaticus. *Chest* 1986; 89:152-154
  14. O'Rourke PP, Crone PK: Halothane in status asthmaticus. *Crit Care Med* 1982; 10:341-343
  15. Saulnier FF, Durocher AV, Deturck RA, et al: Respiratory and hemodynamic effects of halothane in status asthmaticus. *Crit Care Med* 1982; 10:341-343
  16. Pearson J: Prolonged anesthesia with isoflurane. *Anesth Analg* 1985; 64:92-93
  17. Eger EI: Isoflurane: A review. *Anesthesiology* 1981; 55:559-576
  18. Joas TA, Stevens WC: Comparison of the arrhythmic doses of epinephrine during forane, halothane, and fluorene anesthesia in dogs. *Anesthesiology* 1971; 35:48-53
  19. Spencer EM, Willatts SM, Prys-Roberts C: Plasma inorganic fluoride concentrations during and after prolonged (>24 h) isoflurane sedation: Effect on renal function. *Anesth Analg* 1991; 73:731-737
  20. Cheng EY, Kay J, Hopwood M, et al: Effect of prolonged isoflurane anesthesia on urine output and creatinine clearance. *Anesthesiology* 1986; 65:A463
  21. Truog RD, Rice SA: Inorganic fluoride and prolonged isoflurane anesthesia in the intensive care unit. *Anesth Analg* 1989; 69:843-845
  22. Cousins MJ, Mazze RI: Methoxyflurane nephrotoxicity: A study of the dose response in man. *JAMA* 1973; 225:1611-1616
  23. Mazze RI, Calverly RK, Smith NT: Inorganic fluoride nephrotoxicity: prolonged enflurane and halothane anesthesia in volunteers. *Anesthesiology* 1977; 46:265-271
  24. Rice M, Hatherill M, Murdoch IA: Rapid response to isoflurane in refractory status asthmaticus. *Arch Dis Child* 1998; 77:395-396
- Volatile anesthesia gas scavenging system. Our current system uses the hospital ventilation system that is not a semiclosed circuit which would allow for less anesthetic use.

### Monitoring

- The minimum monitoring equipment should include the following:
  - End-tidal CO<sub>2</sub>.
  - Cardiorespiratory support with pulse oximetry.
  - Arterial access for blood pressure and blood gas monitoring.
  - Central venous access for volume status monitoring and delivery of medications.

Consider including the following monitoring devices:

- Paratrend 7 continuous arterial blood gas monitoring system.
- Inline volatile gas analyzer for oxygen, anesthetic, and CO<sub>2</sub> monitoring.

### Medications

- Isoflurane. Start therapy at 1% to 2% and adjust by 0.1% every 5-10 mins to a goal of PIP  $\leq$ 35 cm H<sub>2</sub>O to maintain adequate ventilation as evidenced by Paco<sub>2</sub> <50-60 torr with pH >7.2 with tidal volumes of 8-10 mL/kg. Once a reasonable response has been achieved, maintain the concentration for 2-4 hrs to allow for the reversal of the bronchospastic state before weaning the medication.
- Discontinue sedation and paralytics for isoflurane concentrations >1%. The minimum alveolar concentration of isoflurane is 1.15%. Further sedation and analgesia should be unnecessary at >1 minimum alveolar concentration of an inhaled anesthetic.
- Continue therapy with intravenous terbutaline unless the patient develops ventricular arrhythmias. Isoflurane and  $\beta$ -2 agonists provide bronchodilation by differing mechanisms. The combination of therapeutic agents is likely to provide additive benefits.
- Continue to maintain serum magnesium levels of 3.0-4.0 mg/dL with bolus therapy as needed.
- Continue intravenous corticosteroid

therapy at 4 mg/kg per day methylprednisolone divided every 6 hrs.

### Complications

- Hypotension. This is the most commonly encountered complication of isoflurane therapy. Hypotension should be treated initially with aggressive volume replacement with crystalloid. After 40-60 mL/kg of volume, consider the institution of pressor therapy with either epinephrine at 0.05  $\mu$ g/kg/min or dopamine at 5  $\mu$ g/kg/min, adjusting to desired effect.
- Pneumothorax. Be prepared to deal with this complication of positive pressure ventilation with thoracentesis and chest tube placement.
- Arrhythmias. Follow chemistries to avoid derangements of critical electrolytes, such as potassium, magnesium, and calcium. Tachyarrhythmias may be potentiated by hypercarbia, acidosis, and  $\beta$ -2 agonist therapy. If arrhythmias persist and are life-threatening despite addressing these issues, discontinue isoflurane therapy.
- Nephro/hepatotoxicity. Follow serum electrolytes, blood urea nitrogen/creatinine, liver enzymes, and urine output closely. Changes in any of these variables should be noted, and serum fluoride levels should then be obtained. Consideration for decreasing the dose of inhaled isoflurane should be made if fluoride levels are near 30  $\mu$ M.

### Termination

- Decrease isoflurane by 0.1% every 20-30 minutes for PIP <30 cm H<sub>2</sub>O with tidal volumes  $\geq$ 8 mL/kg and Paco<sub>2</sub> <60 torr with pH >7.2.
- Reinstitution sedation and analgesia as needed for the continuation of positive pressure ventilation when the inhaled concentration of isoflurane is <1%.
- Reinstitution  $\beta$ -2 agonist therapy as the inhaled isoflurane concentration approaches 1% if it had been discontinued.

## APPENDIX

### Isoflurane Protocol

#### Entry Criteria

- Intubated asthmatic requiring peak inspiratory pressures of >40 cm H<sub>2</sub>O to maintain adequate ventilation despite intravenous corticosteroids, magnesium therapy, anticholinergic therapy, and terbutaline at  $\geq$ 5.0 mcg/kg/min iv.

#### Equipment

- Servo 900-D anesthesia ventilatory support or other anesthesia-capable ventilatory support.