

PAEDIATRICS

Sevoflurane therapy for life-threatening asthma in children

D. Schutte^{1*}, A. M. Zwitterloot², R. Houmes³, M. de Hoog³, J. M. Draaisma² and J. Lemson¹

¹ Department of Intensive Care Medicine and ² Department of Paediatrics, Radboud University Nijmegen Medical Centre, PO Box 9101 Nijmegen, 6500 HB, The Netherlands

³ Department of Paediatric Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

* Corresponding author. E-mail: d.schutte@cukz.umcn.nl

Editor's key points

- Children with life-threatening asthma are successfully treated with sevoflurane inhalation therapy without serious side-effects.
- Sevoflurane administration corrects high levels of P_{CO_2} and provides clinical improvement within the first hours.
- Prospective research is required to further explore the position of sevoflurane as rescue medication.

Background. Asthma is a common disease in children and often develops early in life. This multicentre retrospective case series describe the use and effectiveness of sevoflurane inhalation therapy in a series of children with severe asthma in the paediatric intensive care unit (PICU).

Methods. Seven children ranging from 4 to 13 yr of age admitted to the PICU of two tertiary care hospitals in the Netherlands were included. They all were admitted with the diagnosis of severe asthma requiring invasive mechanical ventilation and were treated with sevoflurane inhalation therapy.

Results. The median (range) P_{CO_2} level at the start, after 2 h, and at the end of sevoflurane treatment were 14 (5.1–24.8), 9.8 (5.4–17.0), and 6.2 (4.5–11.4) kPa ($P=0.05$) while the median (range) pH was 7.02 (6.97–7.36), 7.18 (7.04–7.35), and 7.43 (7.15–7.47) kPa ($P=0.01$), respectively. The median (range) peak pressure values declined from 30 (23–56) to 20.4 (14–33) cm H_2O ($P=0.03$). No severe adverse effects besides hypotension, with sufficient response to norepinephrine treatment, were seen.

Conclusions. Sevoflurane inhalation corrects high levels of P_{CO_2} and provides clinical improvement in mechanically ventilated children with life-threatening asthma who fail to respond to conventional treatment.

Keywords: anesthetics, inhalation; asthma; pediatrics; sevoflurane

Accepted for publication: 5 June 2013

Asthma is a common disease in children and often develops early in life. It is a chronic inflammation of the airways, with reversible airflow obstruction and enhanced bronchial reactivity.¹ In Western Europe, the prevalence is 9.7% in children from 6 to 7 yr old and 15.8% in children from 13 to 14 yr old.² Of these children, respectively, 12.6 and 15.2% have severe asthma; ~9% of the children with asthma visit an emergency department while 2% need hospitalization.^{2,3} A severe asthma attack requiring hospitalization is treated with oxygen, corticosteroids, and β_2 -agonists, either nebulized or i.v., in combination with anticholinergic agents and magnesium sulphate. Life-threatening asthma requires invasive interventions like mechanical ventilation and can even be fatal.^{4,5} There is a positive correlation between asthma prevalence in children and the amount of hospital admissions and mortality rate.⁶ It seems, therefore, important to develop more efficient therapies to prevent death in children because of this disease. In 2004, an animal study demonstrated that volatile agents reverse

bronchoconstriction in sensitized guinea pigs.⁷ For several years, inhalation of volatile anaesthetics, such as halothane and isoflurane, have been used as last resort for the treatment of life-threatening asthma in children.^{4, 8–10} These agents provide a reversal of bronchospasm in humans as well, but the exact mechanism of its effect is not clear.¹¹ The proposed mechanisms include lowering of vagal tone, direct relaxation of smooth muscle tissue, inhibition of the release of bronchoconstrictive mediators, and synergy with catecholamines.^{4, 11} Sevoflurane is a newer volatile anaesthetic agent, and is frequently used in children for the induction and maintenance of anaesthesia. It has a low blood to gas solubility coefficient and for this reason provides a rapid and smooth inhaled induction.¹² An animal study showed the beneficial effect of sevoflurane on asthmatic bronchoconstriction, which was later confirmed in humans.^{13–15} We describe a multicentre retrospective case series of the use of sevoflurane therapy in children with asthma on the paediatric intensive care unit (PICU).

Methods

In the PICU database with all patient admission data of two university teaching hospitals, children admitted with asthma over a period of 10 yr (2002–2012) were collected. Children who did not receive mechanical ventilation were excluded. Medical records of the remaining children were analysed. Children who were treated with sevoflurane inhalation therapy with a dedicated anaesthesia system were identified and reviewed. Patient characteristic data, medical history, provocation factor for the current asthma attack, and medication before hospitalization were gathered. To determine the effect of sevoflurane therapy, blood gas and mechanical ventilation parameters, other medication used, and the dose and duration of sevoflurane therapy were collected. Outcomes included clinical improvement of the patient as a subjective measure. Objective measures were improvement of blood gas and mechanical ventilation parameters, and duration of PICU stay. Statistical analysis of the changes in blood gas and mechanical ventilation parameters after administration of sevoflurane was performed with the Mann–Whitney *U*-test and a *P*-value of <0.05 was considered statistically significant.

Results

A total of seven children (age range 4–13 yr) were included. One patient presented with a first exacerbation of asthma and had not been previously diagnosed with this disease. All other patients used daily asthma medication, varying from beclomethason, fluticasone, salmeterol in combination with fluticasone, and montelukast, in combination with salbutamol when necessary. Five patients had no history of hospitalization for asthma exacerbations, and in six children, the asthma attack was triggered because of a viral or bacterial infection. All patients received oxygen and multiple inhalations with salbutamol and ipratropium bromide, followed by i.v. prednisolone, salbutamol, and magnesium sulphate. They showed no improvement of oxygenation and ventilation with the conventional treatment. Because of life-threatening respiratory muscle fatigue or altered mental status, the patients were sedated and intubated with a varying combination of propofol, morphine, rocuronium, esketamine, and midazolam. Sevoflurane treatment was indicated because of respiratory acidosis ($n=5$), hypoxaemia ($n=1$), or a combination ($n=1$). Sevoflurane was administered for a median duration of 24 h, with a range of 0.5–90 h. The peak concentration of sevoflurane ranged from 1 to 8%. Six patients showed an immediate clinical improvement and a progressive correction of blood gas parameters and peak pressures. In Figures 1–3, individual improvement of blood gas parameters is displayed. The first assessment point is 2–3 h after the start of the treatment, except for the patient who only received 0.5 h sevoflurane. The endpoint in the figures varies from 0.5 to 90 h. There was a significant improvement in P_{aCO_2} , pH, and peak pressure at the end of treatment compared with the start. The median (range) P_{aCO_2} levels at the start, at the first assessment, and at the end of sevoflurane treatment were 14 (5.1–24.8), 9.8 (5.4–17.0), and 6.2 (4.5–11.4) kPa ($P=0.05$) while the median

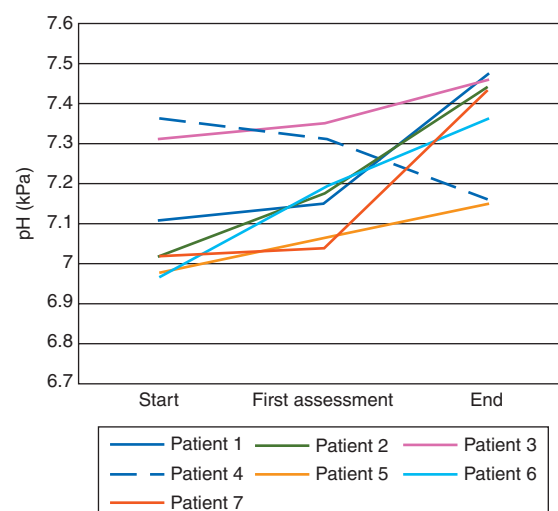


Fig 1 pH values per patient before, after a first assessment, and at the end of treatment with sevoflurane. The dashed line shows the patient who did not respond to sevoflurane therapy.

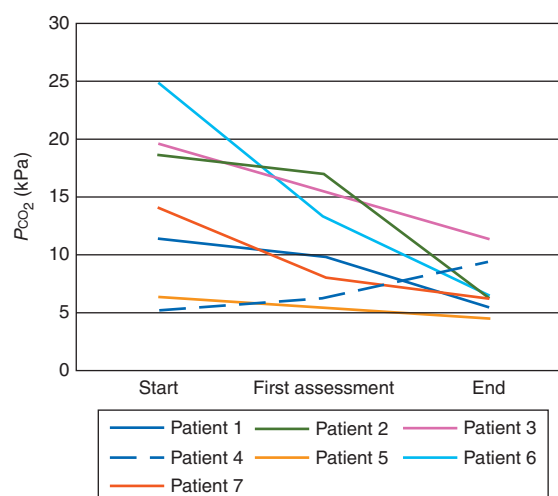
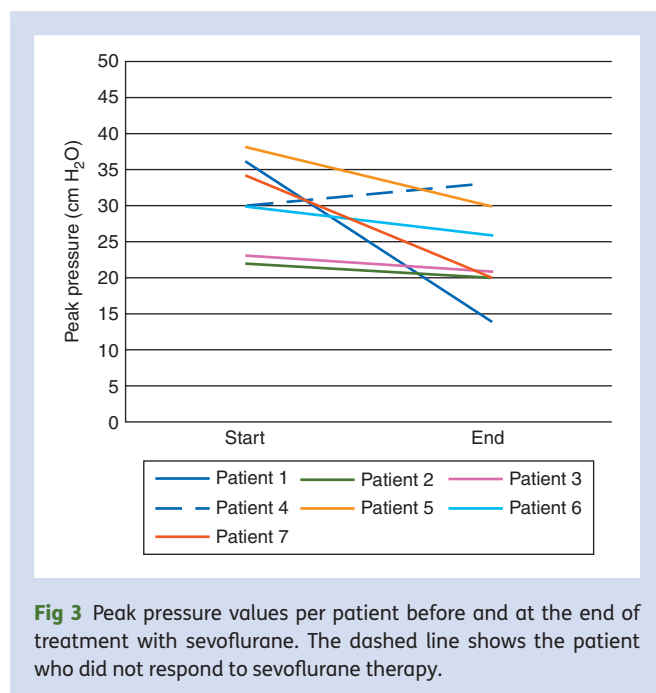


Fig 2 P_{CO_2} values per patient before, after a first assessment, and at the end of treatment with sevoflurane. The dashed line shows the patient who did not respond to sevoflurane therapy.

(range) pH was 7.02 (6.97–7.36), 7.18 (7.04–7.35), and 7.43 (7.15–7.47) kPa ($P=0.01$), respectively. The median (range) peak pressure values normalized from 30 (23–56) to 20.4 (14–33) cm H_2O ($P=0.03$). One patient failed to respond to sevoflurane treatment; afterwards, he was diagnosed with acute respiratory distress syndrome (ARDS). Five patients developed hypotension; of which, four received norepinephrine (0.1–0.6 μg kg h) as vasoactive support, effectively increasing the arterial pressure. One patient had pupils



unreactive to light for a short period. There was no evidence of other complications. The length of PICU stay ranged from 3 to 10 days. All patients survived and were discharged from the hospital within 14 days.

Discussion

This study shows that children with life-threatening asthma are successfully treated with sevoflurane inhalation therapy without serious side-effects. These results are consistent with published single cases.^{14 15} Almost all patients showed a clinical improvement within an hour after administration of sevoflurane. Improved blood gas parameters and peak pressures after 2 h confirm this improvement. All other medication was continued after administration of sevoflurane in equal dosages; therefore, it is very likely that the observed positive effect was induced by sevoflurane. It seems sensible to decrease the dose of sedative drugs during sevoflurane therapy guided by sedation scoring.

One patient in our study did not respond to the therapy. He was afterwards judged to have ARDS related to pneumonia; gas exchange in this patient indeed improved with the inhalation of nitric oxide.

In the past, older volatile anaesthetics have shown to be lifesaving for children with life-threatening asthma with persistent hypercapnia, hypoxaemia, and respiratory acidosis.^{4 7 8} Sevoflurane is a newer anaesthetic, and is safely used in children for the induction and maintenance of anaesthesia. Habre and colleagues described a negative effect of sevoflurane in children with asthma receiving sevoflurane as induction of anaesthesia, it increased the respiratory system resistance.¹² However, others described beneficial effects in which sevoflurane caused a greater decrease in airway resistance compared with

halothane or isoflurane.^{16–18} Furthermore, sevoflurane provides a favourable haemodynamic profile, a lower metabolic rate, and most importantly increased bronchodilator properties and less adverse effects than the older anaesthetic volatile agents.^{9 13 16 18}

In the treatment of our patients, there was a variation in the dose of sevoflurane from 1 to 8%; the duration of administration varied from 0.5 to 90 h. This variation can be explained by patient factors, such as the age, severity of and duration of the asthma attack, and by preference or experience of the treating physician. Dose and duration should be individually titrated to effect. High-dose sevoflurane can have several adverse effects. Epileptiform activity is seen in electroencephalograms, which is occasionally accompanied by clinical manifestation of seizures, however without clinical sequelae.¹¹ Furthermore, there can be a dose-related effect on arterial pressure and heart rate. Theoretically, sevoflurane is associated with nephrotoxicity related to the release of fluoride during metabolism, but clinical signs of nephrotoxicity are rare.⁸ Hepatotoxicity is an important adverse effect of the other volatile anaesthetics, related to immune-mediated hepatitis caused by trifluoroacetic acid (TFA), a metabolic product. Sevoflurane is metabolized in a different way than the other agents and does not produce TFA and thereby does not cause hepatotoxicity.¹¹ The only adverse effect we observed was hypotension but that was successfully treated with norepinephrine. One patient had pupils unreactive to light for a short period; no other symptoms of neuropathy occurred. We cannot explain this symptom, but it is known that nebulized ipratropium bromide sometimes causes this effect.^{19 20} The patient received multiple doses of nebulized ipratropium and salbutamol as first treatment modality.

One drawback for the use of sevoflurane is the introduction of an anaesthesia machine on the PICU. Most PICUs do not have the equipment needed for the safe delivery of sevoflurane, the technology is often not known to the PICU personnel, and exhaled gas evacuation is mandatory. All PICUs should consider procuring such options and cooperate with the local anaesthesia department. There has been a report where sevoflurane is used in combination with non-invasive ventilation.²¹ However, since children with very severe asthma are already intubated, this will not be possible in these children. On the other hand, in less severe cases, it is questionable if the cost-benefit of administering sevoflurane by a face mask is more beneficial compared with salbutamol inhalation or i.v. therapy.

Although there are limitations of our study, like the retrospective nature, the chance of missing a few patients because of the retrospective nature, and the small number of patients, we conclude that sevoflurane should be considered as rescue therapy in children with life-threatening asthma who fail to respond to conventional treatment.

Authors' contributions

D.S. designed the study, collected the data, performed all statistics, wrote the manuscript, and approved the final manuscript as submitted. A.M.Z. assisted in the design of the study and

assisted in the writing of the manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted. M.H. provided the data of some of the patients, reviewed and revised the manuscript, and approved the final manuscript as submitted. R.H. provided the data of some of the patients, reviewed and revised the manuscript, and approved the final manuscript as submitted. J.M.D. reviewed and revised the manuscript, and approved the final manuscript as submitted. J.L. assisted in the writing of the manuscript, supervised the study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Declaration of interest

None declared.

Funding

No external funding was obtained for this study.

References

- 1 *The Global Asthma Report 2011*. Paris: The International Union Against Tuberculosis and Lung Disease, 2011
- 2 Lai CKW, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009; **64**: 476–83
- 3 Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005–2009. *Centers for Disease Control and Prevention National Center for Health Statistics Report*, No. 32, 2011
- 4 Koninckx M, Buysse CMP, De Hoog M. Management of status asthmaticus in children. *Paediatr Respir Rev* 2013; **14**: 78–85
- 5 Roberts JS, Bratton SL, Brogan TV. Acute severe asthma: differences in therapies and outcomes among paediatric intensive care units. *Crit Care Med* 2002; **30**: 581–5
- 6 Anderson HR, Gupta R, Kapetanakis V, et al. International correlations between indicators of prevalence, hospital admissions and mortality for asthma in children. *Int J Epidemiol* 2008; **37**: 573–82
- 7 Schütz N, Peták F, Barazzzone-Argiroffo C, Fontao F, Habre W. Effects of volatile anaesthetic agents on enhanced airway tone in sensitized guinea pigs. *Br J Anaesth* 2004; **92**: 254–60
- 8 Restrepo RD, Pettignano R, DeMeuse P. Halothane, an effective infrequently used drug, in the treatment of paediatric status asthmaticus: a case report. *J Asthma* 2005; **42**: 649–51
- 9 Shankar V, Churchwell KB, Deshpande JK. Isoflurane therapy for severe refractory status asthmaticus in children. *Intensive Care Med* 2006; **32**: 927–33
- 10 Turner DA, Heitz D, Cooper MK, Smith PB, Arnold JH, Bateman ST. Isoflurane for life-threatening bronchospasm: a 15-year single-center experience. *Respir Care* 2012; **57**: 1857–64
- 11 Tobias JD. Inhalation anesthesia: basic pharmacology, end organ effects, and applications in the treatment of status asthmaticus. *J Int Care Med* 2009; **24**: 361–71
- 12 Habre W, Scalfaro P, Sims C, Tiller K, Sly PD. Respiratory mechanics during sevoflurane anesthesia in children with and without asthma. *Anesth Analg* 1999; **89**: 1177–81
- 13 Burburan SM, Xisto DG, Ferreira HC, et al. Lung mechanics and histology during sevoflurane anesthesia in a model of chronic allergic asthma. *Anesth Analg* 2007; **104**: 631–7
- 14 Watanabe K, Mizutani T, Yamashita S, Tatekawa Y, Jinbo T, Tanaka M. Prolonged sevoflurane inhalation therapy for status asthmaticus in an infant. *Paediatr Anesth* 2008; **18**: 543–5
- 15 Schultz TE. Sevoflurane administration in status asthmaticus: a case report. *AANA J* 2005; **73**: 35–6
- 16 Rooke GA, Choi JH, Bishop MJ. The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation. *Anesthesiology* 1997; **86**: 1294–9
- 17 Holzman RS, van der Velde ME, Kaus SJ, et al. Sevoflurane depresses myocardial contractility less than halothane during induction of anesthesia in children. *Anesthesiology* 1996; **85**: 1260–7
- 18 von Ungern-Sternberg BS, Saudan S, Petak F, Hantos Z, Habre W. Desflurane but not sevoflurane impair airway and respiratory tissue mechanics in children with susceptible airways. *Anesthesiology* 2008; **108**: 216–24
- 19 Watson WT, Shuckett EP, Becker AB, Simons FE. Effect of nebulised ipratropium bromide on intraocular pressures in children. *Chest* 1994; **105**: 1439–41
- 20 Woelfe J, Zielen S, Lentze MJ. Unilateral fixed dilated pupil in an infant after inhalation of nebulised ipratropium bromide. *J Pediatr* 2000; **136**: 423–4
- 21 Carron M, Freo U, Ori C. Subanaesthetic sevoflurane by a helmet for bronchospasm after tracheal extubation. *Br J Anaesth* 2009; **103**: 307–8

Handling editor: M. M. R. F. Struys