Sevoflurane therapy for life-threatening acute severe asthma: a case report

Traitement par sevoflurane pour asthme aigu grave avec risque de décès : un rapport de cas

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Abstract

Introduction Acute severe asthma is a life-threatening form of bronchial constriction in which the progressively worsening airway obstruction is unresponsive to the usual appropriate bronchodilator therapy. Pathophysiological changes restrict airflow, which leads to premature closure of the airway on expiration, impaired gas exchange, and dynamic hyperinflation (“air-trapping”). Additionally, patients suffering from asthma for a prolonged period of time usually have serious comorbidities. These conditions constitute a challenge during the treatment of this disease. Therapeutic interventions are designed to reduce airway resistance and improve respiratory status. To achieve therapeutic goals, appropriate bronchodilator treatment is indispensable, and mechanical ventilation under adequate sedation may also be required. The volatile anesthetic agent, sevoflurane, meets both criteria; therefore, its use can be beneficial and should be considered.

Case presentation A 67-yr-old Caucasian male presented with acute life-threatening asthma provoked by an assumed upper airway infection and non-steroidal anti-

inflammatory drug antipyretics, complicated by chronic atrial fibrillation and hemodynamic instability. Due to frequent premature ventricular contractions, conventional treatment was considered unsafe and discontinued, and sevoflurane inhalation was initiated via the AnaConDaTM (Anaesthetic Conserving Device). Symptoms of life-threatening bronchospasm resolved, and the patient's respiratory status improved within hours. Adequate sedation was also achieved without any hemodynamic adverse effects.

Conclusion The volatile anesthetic agent, sevoflurane, is used widely in anesthesia practice. Its utility for treatment of refractory bronchospasm has been appreciated for years; however, its administration was difficult within the environment of the intensive care unit due to the need for an anesthesia machine and a scavenging system. The introduction of the AnaConDa eliminates these obstacles and makes the use of sevoflurane safe and simple. Our case report reveals the potential of sevoflurane as a “two-in-one” (bronchodilator and sedative) drug to treat a severe acute asthma attack.

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Résumé

Introduction Une crise d'asthme aigu grave représente une forme de constriction bronchique pouvant mettre la vie en danger, au cours de laquelle l'aggravation progressive de l'obstruction de la voie respiratoire ne répond pas au traitement bronchodilatateur adéquat habituel. Des modifications physiopathologiques réduisent le débit d'air, aboutissant à une fermeture prématurée de la voie respiratoire pendant l'expiration, une altération des échanges gazeux, un hypergonflement dynamique (« trappage » ou piégeage de l'air). De plus, des patients souffrant d'asthme pendant une période prolongée présentent habituellement des comorbidités graves. Ces

affections constituent un véritable défi au cours du traitement de cette maladie. Les interventions thérapeutiques sont destinées à réduire la résistance à l'air et améliorer le statut respiratoire. Pour atteindre ces objectifs thérapeutiques, un traitement bronchodilatateur adapté est indispensable et une ventilation mécanique sous sédation adéquate peut également être nécessaire. Un agent anesthésique volatil, le sévoflurane, répond à ces deux critères; son utilisation peut, par conséquent, être bénéfique et doit être envisagée.

Présentation du cas Un homme caucasien de 67 ans s'est présenté avec une crise aiguë d'asthme le mettant à risque de décès; la crise a été provoquée par une infection supposée des voies aériennes hautes et des médicaments antipyrétiques de type anti-inflammatoires non stéroïdiens, et compliquée par une fibrillation auriculaire chronique et une instabilité hémodynamique. Compte tenu de la fréquence de contractions ventriculaires prématurées, le traitement conventionnel a été jugé peu sûr et a été interrompu; une inhalation de sévoflurane a été entreprise en utilisant le dispositif AnaConDaTM (dispositif de chambre de rétention de l'anesthésique). Les symptômes du bronchospasme menaçant le pronostic vital ont disparu et l'état respiratoire du patient s'est amélioré en quelques heures. Une sédation adéquate a été également obtenue sans effets indésirables.

Conclusion Le sévoflurane, un agent anesthésique volatil, est largement utilisé en pratique anesthésique. Son intérêt pour le traitement du bronchospasme réfractaire est apprécié depuis des années; toutefois, son administration était difficile dans le cadre d'une unité de soins intensifs en raison de la nécessité de disposer d'une machine d'anesthésie et d'un système d'évacuation. L'introduction de l'AnaConDa élimine ces obstacles et rend l'utilisation du sévoflurane simple et sécuritaire. Notre observation révèle le potentiel de médicament « deux-en-un » du sévoflurane (bronchodilatateur et sédatif) pour le traitement de la crise d'asthme aigu grave.

Asthma is a disease of predominantly reversible airway obstruction characterized by a triad of bronchospasm, airway inflammation, and increased secretions. It is a major healthcare problem for both sexes and all age groups, with a prevalence of 2-18% in the European population.¹⁻³

Acute exacerbations are often precipitated by viral or bacterial infections, excessive allergen exposure, and adverse side effects of drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]), although the causes often remain unknown.

An acute severe asthma attack is a life-threatening presentation of the disease characterized by progressively increasing intrinsic positive end-expiratory pressure (PEEPi), “air-trapping”, and dynamic hyperinflation of the lungs leading to impaired gas exchange.^{3,4}

Standard medical treatment is based on oxygen inhalation with a high fraction of inspired oxygen (F_IO₂) and nebulized or intravenous bronchodilators. In case of deterioration, noninvasive or invasive mechanical ventilation may be required, and adequate sedation (and if necessary, initiation of a neuromuscular blockade) is essential to achieve therapeutic goals. The drugs of choice are usually intravenous anesthetics; however, either the potential histamine-releasing effect of opioids or the hallucinations and nightmares caused by ketamine should always be considered.^{2,3}

Volatile anesthetics (e.g., sevoflurane and isoflurane) are effective bronchodilators, and their use is associated with reductions in PEEPi and arterial carbon dioxide tension (PaCO₂) within hours. Their “two-in-one effect” indicates that their use could be a good alternative for the standard treatment.⁵⁻¹¹ There are two potential problems with the use of these agents within the intensive care unit (ICU) environment: hypotension is their principle side effect, and delivery (and scavenging of the exhausted gas mixture) of these agents by standard ICU ventilators may be difficult. Hypotension is not usually encountered with volatile agents used in sedative doses. The AnaConDaTM (Anaesthetic Conserving Device; Sedana Medical, Uppsala, Sweden) makes it possible to deliver anesthetic agents easily and safely with any standard ventilator. The AnaConDa contains a bacterial and heat-and-moisture-exchanger (HME) filter and a small but high-capacity miniature vaporizer with a high-efficiency conserving medium (active carbon) that is supplied continuously by any type of syringe pump (Fig. 1). The device is inserted between the endotracheal tube and the Y-piece of the ventilator circuit, and the inhaled and exhaled concentrations of anesthetic agent can be measured by a gas monitor (Fig. 2). During expiration, air passes over the active carbon, into the ventilator circuit, and out through the ventilator exhaust while the anesthetic agent is adsorbed to the active carbon. In contrast, during inspiration, the anesthetic agent is transported with the inhaled gas to the patient together with agent evaporated from the miniature vaporizer. With this unique technique, approximately 90% of the delivered agent can be recycled, obviating the need for any active scavenging system and making the treatment safe and cost effective.¹²⁻¹⁴ Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Fig. 1 AnaConDa (Anaesthetic Conserving Device) On top: Schematic structure of the AnaConDa (explanation in the text). Bottom left: A special syringe (included in package) filled with sevoflurane connected to the agent line of the AnaConDa in a syringe pump. Bottom right: Connecting the AnaConDa into the breathing circuit; on the right ventilator side, it is connected to the Y-piece of the breathing circuit, and on the left patient side, it is connected to the endotracheal tube, and the gas monitor line is also attached

Fig. 2 Setup of the AnaConDa Patient side is attached to the endotracheal tube; ventilator side is connected to the Y-piece of the breathing circuit. The inhalational anesthetic agent is delivered by the agent supply line connected to the syringe (included in the set) filled with the anesthetic agent, which is delivered by any syringe pump system. The inhaled and exhaled anesthetic agent concentration levels are measured by connecting a monitor to the gas monitor port. The ventilator can be equipped optionally with a special scavenging system

Case presentation

A 67-yr-old Caucasian male presented with acute life-threatening asthma provoked by an assumed upper airway infection and NSAID antipyretics, complicated by chronic atrial fibrillation and hemodynamic instability.

His medical history included a tonsillectomy as a child, bronchial asthma for 30 years, chronic obstructive pulmonary disease, allergic rhinitis, nasal polyps, and

antiarrhythmic and oral anticoagulant treatment due to chronic atrial fibrillation (after unsuccessful attempts at cardioversion). He had consumed alcohol regularly but never smoked. His medications included verapamil (to control heart rate), acenocoumarol, budesonide/formoterol, and salbutamol.

Two days before his admission, the patient had fever, cough, signs of upper airway infection, and progressively worsening shortness of breath unresponsive to inhalational

Table 1 Arterial blood gas samples

Parameters	Results	
	Pulmonology centre	ICU admission
PaO ₂ (mmHg)	74	182
PaCO ₂ (mmHg)	59	71
pH	7.23	7.229
BE (mEq·L ⁻¹)	-1.2	-1.0
stHCO ₃ ⁻ (mEq·L ⁻¹)	24.3	23
seLac (mEq·L ⁻¹)	2.1	1.8

ICU = intensive care unit; PaO₂ = arterial oxygen tension; PaCO₂ = arterial carbon dioxide tension; pH = acidity; BE = base excess; stHCO₃⁻ = standard hydrogen carbonate concentration; seLac = serum lactate concentration

bronchodilators. After taking 500 mg of acetylsalicylic acid, dyspnea became unbearable, and his wife called an ambulance. In spite of adequate pre-hospital treatment (oxygen inhalation, bronchodilators, corticosteroids, and fluid supplementation), his SpO₂ remained at 76–80%, which resulted in his admission to the noninvasive ventilation unit of the Pulmonology Centre. Laboratory tests showed discrete elevation of inflammatory markers: C-reactive protein (CRP) = 18.5 mg·L⁻¹, procalcitonin (PCT) = 0.6 µg·L⁻¹, high international normalized ratio = 3.26, and normal white blood cell count (WBC) = 8.3 g·L⁻¹ without any infiltration on the chest *x-ray* and no signs of cardiac ischemia on the electrocardiogram. His arterial blood gas (ABG) sampling indicated hypoxemia, hypercapnia, and respiratory acidosis (Table 1). Broad-spectrum antibiotics, bronchodilator and mucolytic treatment, and noninvasive ventilation were initiated. Due to rapid deterioration of his condition and a worsening mental status, endotracheal intubation and invasive mechanical ventilation were performed (intermittent positive pressure ventilation, PEEP = 5 cmH₂O, peak airway pressure (P_{peak}) = 60 cmH₂O,

Fig. 3 Initiation of sevoflurane therapy using the AnaConDa A syringe filled with sevoflurane is inserted in a syringe pump delivering sevoflurane 4.5 mL·hr⁻¹ (right upper corner). The gas monitor (connected to the patient side) shows the anesthetic agent concentration levels, respiratory rate = 12 breaths·min⁻¹, and the MAC of sevoflurane = 0.4 (right lower corner)

V_{tidal} = 450 mL, frequency = 16 breaths·min⁻¹, F_IO₂ = 80–90%), and he was transferred to our ICU.

On ICU admission, the patient had a temperature of 36.8°C, a tachyarrhythmia (heart rate fluctuating between 120–140 beats·min⁻¹), a blood pressure 90–100/70 mmHg, and an oxygen saturation of 96% on F_IO₂ 80%. Bilateral wheezing was heard on auscultation, and signs of hyperinflation were seen, indicating minimal response to standard treatment. He was deeply sedated with propofol to a Richmond Agitation Sedation Scale (RASS) of -5. The remainder of the physical examination was within normal limits.

Urgent ABG (Table 1) and tracheal secretions for microbiological testing were taken. Additionally, corticosteroids, mucolytics, broad-spectrum antibiotics, and intravenous insulin for glucose control were

Table 2 Airway parameters measured by ICU ventilator during treatment

Parameters	Results		
	On admission	30 min after initiation of sevoflurane	28 hr after initiation of sevoflurane
Compl (mL·cmH ₂ O ⁻¹)	17.2	47.7	116
R _{insp} (cmH ₂ O·L ⁻¹ ·sec ⁻¹)	21	49	3
R _{exp} (cmH ₂ O·L ⁻¹ ·sec ⁻¹)	30	19	6
P _{peak} (cmH ₂ O)	60	36	15
PEEP _i (cmH ₂ O)	11	3.2	3
F _I O ₂ (%)	80	55	40

ICU = intensive care unit; Compl = airway compliance; R_{insp} = inspiratory resistance; R_{exp} = expiratory resistance; P_{peak} = peak airway pressure; PEEP_i = intrinsic positive end-expiratory pressure; F_IO₂ = fraction of inspired oxygen

Table 3 Results of laboratory tests performed during treatment

Laboratory test	Results			
	On admission	24 hr after admission	36 hr after admission	48 hr after admission
WBC ($\text{g}\cdot\text{L}^{-1}$)	8.3	6.6	8.2	10.0
Plt ($\text{g}\cdot\text{L}^{-1}$)	125	113	120	174
CRP ($\text{mg}\cdot\text{L}^{-1}$)	18.5	10	8	8
PCT ($\mu\text{g}\cdot\text{L}^{-1}$)	0.6	0.5	0.5	0.2
seCreat ($\mu\text{Mol}\cdot\text{L}^{-1}$)	95	86	75	67
BUN ($\text{mMol}\cdot\text{L}^{-1}$)	6	4.7	5.2	7.1
seBi ($\mu\text{Mol}\cdot\text{L}^{-1}$)	10	8	9	8

BUN = blood urea nitrogen; CRP = C-reactive protein; PCT = procalcitonin; Plt = platelet count; seBi = serum bilirubin; seCreat = serum creatinin; WBC = white blood cell count

continued. Airway parameters measured by the Hamilton Galileo-CI ventilator (Hamilton Medical AG, Bonaduz, Switzerland) showed extremely limited airflow (Table 2). DuoPAP mode ventilation support was started with a prolonged expiratory time (I:E ratio 1:4.5) and moderate PEEP (12 cmH_2O) according to PEEP_i.

As conventional treatment was ineffective, we decided to use an alternative therapy. An AnaConDa was inserted into the ventilator circuit and sevoflurane therapy was initiated (Fresenius Orchestra Module DPS syringe pump, Fresenius Kabi Ltd., Bad Homburg, Germany). The inhaled and exhaled sevoflurane concentrations were monitored using the Mindray PM-6000 multi-gas module (Mindray Medical International Ltd., Shenzhen, China) and capnography was also performed (Fig. 3). The target exhaled sevoflurane concentration of 0.5–0.8 v/v% (MAC = 0.4–0.6) was achieved using a syringe pump rate of 3–7 $\text{mL}\cdot\text{hr}^{-1}$.

Thirty minutes after initiating the treatment, airway compliance improved while expiratory resistance and PEEP_i decreased (Table 2). In addition, ventilatory support could be decreased (PEEP = 7 cmH_2O , P_{peak} = 28 cmH_2O , $\text{F}_{\text{I}\text{O}_2}$ = 40%, I:E ratio = 1:3), gas exchange improved, and heart rate normalized without hypotension. Sevoflurane, at this therapeutic dose achieved satisfactory sedation (RASS of −1 –1), and neuromuscular blockade was not required.

Twelve hours later, with stable hemodynamics, intravenous terbutaline and theophylline were given; verapamil was restarted and while sevoflurane sedation was withdrawn gradually during the next 18 hr, low-dose dexmedetomidine was initiated. A follow-up chest *x-ray* did not reveal any infiltrates, inflammatory markers (CRP and PCT) were not elevated, WBC was within normal range, and the tracheal secretions showed no growth. Kidney and liver abnormalities were not detected (Table 3).

Despite regular airway suctioning, the HME filter of the conserving medium became contaminated with respiratory secretions, which resulted in CO_2 retention, and a new AnaConDa had to be placed after 20 hr. After 28 hr, our patient's respiratory status improved significantly (Table 2), wheezing disappeared, and oxygenation was excellent under spontaneous pressure support ventilation (PSV; PEEP = 3 cmH_2O , P_{peak} = 22 cmH_2O , expiratory triggering sensitivity = 35%); therefore, sevoflurane was discontinued. Pressure support could be gradually decreased to 8–10 cmH_2O , and his trachea was extubated six hours later.

For the next two days, a physiotherapist educated the patient on how to perform breathing exercises, intermittent noninvasive ventilation support (PEEP = 0–3 cmH_2O , PSV = 5–8 cmH_2O , $\text{F}_{\text{I}\text{O}_2}$ = 30%) was performed, antibiotics and dexmedetomidine were discontinued, with background therapy (regular inhalational bronchodilators - budesonide/formoterol and salbutamol) continued. On the fifth day of treatment, he was discharged from the ICU to the ward.

Discussion

In cases of refractory bronchospasm, the main therapeutic target is to reduce airway resistance and thus improve respiratory status. To achieve this goal, appropriate bronchodilator treatment is essential; also, mechanical ventilation under adequate sedation may be required.

The patient's comorbidities, regular medications, and clinical status must be taken into consideration since standard therapy might be hazardous or even harmful in some cases. Use of volatile agents in the treatment of refractory status asthmaticus will help to achieve two therapeutic goals: bronchodilation and sedation. Additionally, fewer side effects and drug interactions

Table 4 Signs, symptoms, and treatment of malignant hyperthermia

Signs and symptoms	
Extreme and rapid rise in body temperature – hyperpyrexia ($T_{\text{core}} > 38.8^{\circ}\text{C}$)	
Sweating and flushed skin	
Altered mental state (unexplained confusion, stupor or coma)	
Painful muscles and muscle rigidity especially in the jaw - trismus (masseter muscle rigidity) is usually the first sign	
Increased heart rate – cardiac arrhythmias (unexplained SVT, VT or even VF)	
Hemodynamic instability – low blood pressure or shock	
Increased breathing rate – tachypnea	
Progressively elevating EtCO_2 (> 55 mmHg)	
Increased oxygen consumption	
Respiratory and metabolic acidosis ($\text{PaCO}_2 > 60$ mmHg, $\text{pH} < 7.25$, $\text{BE} < -8$ mEq·L ⁻¹)	
Cola coloured urine due to rhabdomyolysis	
Acute kidney injury (decreasing urine output and increasing serum creatinine levels)	
Treatment	
<i>Specific treatment</i>	Immediate discontinuation of triggering agent Replacing breathing circuit and even ventilator Administration of intravenous dantrolene sodium
<i>Supportive therapy</i>	Mechanical ventilation support Adequate sedation and analgesia Excessive intravenous fluid supplementation Cooling – active and / or passive Hemodynamic support (vasopressors, positive inotropic agents) Treatment of hyperkalemia Renal replacement therapy (hemodialysis)

BE = base excess; EtCO_2 = end-tidal carbon dioxide tension; PaCO_2 = arterial carbon dioxide tension; pH = acidity; SVT = supraventricular tachycardia; T_{core} = core temperature; VF = ventricular fibrillation; VT = ventricular tachycardia

may be expected and cost of treatment may be reduced. Further advantages, including rapid onset of action; no risk of addiction, tolerance and accumulation; and a short wake-up time even after prolonged administration, make their use as first-line drugs worth considering in cases of severe asthma.

Administration of volatile anesthetics via AnaConDa is safe and effective with only a ventilator, a syringe pump, and a gas monitor necessary for its application (Fig. 2). According to the device's principle of operation, only minute ventilation influences the concentration of anesthetic agent in the airway. This is an important point since changes in minute ventilation (e.g., due to improved or even worsening respiratory status) alter the inhaled and exhaled concentration of volatile anesthetics; therefore, it should be closely monitored, and the syringe infusion rate should be readjusted accordingly.

In our case, adequate bronchodilation and sedation was achieved by 0.5–0.8 v/v% of exhaled sevoflurane ($\text{MAC} = 0.4\text{--}0.6$) and no hemodynamic side effects occurred.

Although the bronchodilatory effects of volatile anesthetics have been well known for decades, only a few publications describe their use in refractory bronchospasm. Padkin *et al.* successfully treated a patient with severe exacerbation of asthma by delivering a subanesthetic dose of halothane in 100% oxygen using a close-fitting face mask.⁶ In 2003, Baigel, described a case series about the management of six awake spontaneously breathing patients with acute refractory asthma. In his case report, only one patient required mechanical ventilation support after initial response.⁷ Weber *et al.* presented a case of a ten-year-old boy with severe unresponsive asthma treated with sevoflurane. Although they used an anesthesia machine, the main message of their case report is that the use of inhalational anesthetics should be considered an early treatment option in ventilated asthmatic patients.⁹ The use of AnaConDa in asthma has been previously described and yield similar results to our report. The main difference was the choice of drug: Nickel *et al.* used halothane; Thomson's team used isoflurane, and Nadaud administered a helium-sevoflurane gas mixture.^{8,10,11}

The AnaConDa must be replaced every 24 hr to avoid the risk of occlusion and bacterial growth. A large amount of respiratory secretions, as seen in bronchial asthma, may shorten the lifetime of the device. In our experience, these respiratory secretions can lead to occlusion of the HME filter and therefore needs to be monitored closely. Regular airway suctioning (closed-loop technique is preferable), continuous capnography, and careful monitoring are essential during the use of this device.

Data from clinical studies suggest that there is a potential for renal injury associated with the use of sevoflurane. Some studies show that prolonged use of sevoflurane, even if the fresh gas flow rate is $< 2 \text{ L} \cdot \text{min}^{-1}$, may lead to proteinuria and glycosuria.¹⁵ These side effects are presumed due to Compound A, a degradant produced during interaction between soda lime and sevoflurane.¹⁶ The AnaConDa eliminates this problem because soda lime isn't included in the system. Another aspect that should be considered is that cytochrome P450 2E1 (CYP2E1) metabolizes approximately 5% of sevoflurane to hexafluoroisopropanol (HFIP) with release of inorganic fluoride.^{17,18} Hexafluoroisopropanol is rapidly conjugated with glucuronic acid and eliminated as a urinary metabolite. The clinical impact of conjugated HFIP and fluoride ion production is not clearly evaluated.¹⁹⁻²¹ In our case, we did not find disturbances in kidney or liver function, after 30 hr of sevoflurane exposure.

The third important aspect is the potential for air pollution and exposure of the medical staff to sevoflurane. Despite the manufacturer's recommendation for a gas scavenging system, environmental investigations suggest that an active scavenging system or continuous suctioning of an exhaled gas mixture is unnecessary and that the use of this system is harmless both for the environment and personnel. Djafari Marbini *et al.* measured very low concentrations of volatile anesthetics at various locations around the patient bedside. Only 2-33 parts per million (ppm) during a 12-hr shift were detected (highest values were measured 3 cm adjacent to the ventilator exhaust port).¹⁴ In another study, spectrophotometric measurements showed 0.1-0.2 ppm at 50 cm from the patient's head. These values are significantly below internationally recommended exposure limits.¹²⁻¹⁴ Nevertheless, a special scavenging system (CONTRAfluranTM) is available, and its use seems to be sufficient.²²

Finally, signs of MH should always be monitored and therapy stopped if this complication develops. Administration of intravenous dantrolene sodium and application of supportive therapy may also be required (Table 4).

Conclusion

Although some guidelines on the treatment of severe asthma suggest the use of inhalational anesthetic agents when the usual appropriate therapy is unsuccessful, sevoflurane is not mentioned as a first-line drug. Based on our case report, sevoflurane inhalation via the AnaConDa should be considered is a viable treatment option where patients are refractory to first line treatment. The main benefits of inhalational agents are the simultaneous characteristics of sedation and bronchodilation, the prompt onset of action, and the rapid offset after discontinuation without residual effects, tolerance, or withdrawal syndrome. The AnaConDa makes the dosage of sevoflurane safe, easily modified, extremely simple, and cost effective.

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