

Inhaled and intravenous treatment in acute severe and life-threatening asthma

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Editor's key points

- Current guidelines do not adequately cover the management of life-threatening acute asthma.
- The author has produced a narrative review.
- The author has recommended a plan to manage life-threatening asthma.

Summary. Management of life-threatening acute severe asthma in children and adults may require anaesthetic and intensive care. The inhaled route for drug delivery is not appropriate when only small respiratory gas volumes are shifted; the i.v. route may be associated with greater side-effects. Magnesium sulphate i.v. has a place in acute asthma management because it is a mild bronchodilator, and has a stabilizing effect on the atria which may attenuate tachycardia occurring after inhaled and i.v. salbutamol. If intubation and ventilation are required, a reduction in bronchoconstriction by any means before and during these procedures should reduce morbidity. This narrative review aims to show strengths and weakness of the evidence, present controversies, and forward opinions of the author. The review contains a practical guide to the setting up, use and efficiency of nebulizers, metered dose inhalers, and spacers (chambers). It also presents a commonsense approach to the management of severe asthmatics in whom delay in bronchodilatation would cause clinical deterioration. When self-inhaled agents have had no effect, i.v. drugs may help avoid intubation and ventilation. The review includes suggestions for the use of inhaled anaesthetics, anaesthetic induction, and brief notes on subsequent ventilation of the lungs.

Keywords: asthma; bronchospasm; inhaled anaesthetics; life-threatening

Hospital treatment of acute severe asthma relies on pressurized metered dose inhalers (MDIs) and/or oxygen-driven disposable nebulizers for delivery of short-acting β_2 agonist drugs (SABA) and ipratropium bromide to the lungs, and oral or parenteral steroids. Nebulized or intravenous magnesium sulphate, intravenous aminophylline, intravenous β_2 -agonists, and subcutaneous or intravenous epinephrine are additional therapies. If an asthmatic is unable to speak or breathe in adequate volumes, inhalation therapy is unlikely to reverse bronchospasm. The use of i.v. drugs is recommended in patients in whom inhaled therapy cannot be used; however, there have been no studies of the efficacy of i.v. drugs in such situations.

If treatment fails and asthma becomes life-threatening, anaesthetic and intensive care is required for intubation and ventilation, which are associated with high morbidity and mortality.¹ The British Thoracic Society (BTS/SIGN),² National Institutes of Health (USA, EPR-3),³ and National Asthma Council Australia⁴ guidelines offer little or no information when life-threatened or moribund asthmatics need further treatment. Hence experience, anecdotal case reports, and advice from other physicians must be used to achieve a successful outcome. The author searched the literature including many references cited in asthma guidelines, the Cochrane reviews for β_2 agonists and magnesium sulphate, and obstetric and cardiology literature related to the use of β_2 agonists and magnesium.

This narrative review presents mechanisms, routes for delivery, speed of delivery, and side-effects of bronchodilating

drugs, which may help determine best management of the patients well before or when asthma becomes life-threatening. In addition, suggestions have been made regarding indications and use of inhaled anaesthetic agents in acute asthma.

Asthma definition

Asthma is a chronic inflammatory disorder of the airways. Inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing particularly at night and early morning. Variable airflow obstruction is often reversible either spontaneously or with treatment. Inflammation causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli. Airway obstruction is the result of contraction of airway smooth muscle and swelling of the airway due to smooth muscle hypertrophy and hyperplasia, inflammatory cell infiltration, oedema, goblet cell and mucous gland hyperplasia, mucous hypersecretion, protein deposition including collagen, and epithelial desquamation.⁴

Inhaled routes

The National Institutes of Health Guidelines 2007(USA) state: 'Albuterol (salbutamol) is the preferred short-acting beta2-agonist because it has an excellent safety profile and the most data related to safety during human pregnancy are available for this medication'. BTS/SIGN 2011 guidelines

state: 'There is no evidence for any difference in efficacy between salbutamol or terbutaline (inhaled or intravenous)'.

Salbutamol is a long-acting relatively selective β_2 receptor agonist. Smooth muscle relaxation occurs by stimulation of membrane-bound adenyl cyclase in the presence of magnesium ions to increase cellular levels of cyclic AMP. These levels are thought to inhibit the entry of calcium ions into the cells, therefore inhibiting smooth muscle contraction. High levels of cyclic AMP in mast cells may inhibit histamine and slow-reacting substance-A release. Other peripheral β_2 effects are vasodilatation, skeletal muscle tremor, uterine muscle relaxation, hyperglycaemia, and hypokalaemia. β_1 stimulation causes a tachycardia.

Pressurized MDIs and disposable jet (wet) nebulizers

Pressurized MDIs of salbutamol deliver 100 μg per puff and are best delivered through a volumatic spacer or self-triggered device, and rely on the patient's ability to inhale; 20–40 puffs may be required to reverse bronchoconstriction.² Because chlorofluorocarbon (CFC) propellant reduces the world's ozone layer, it has been replaced by HFA-134a, norflurane, a weak anaesthetic agent with a similar chemical structure to halothane, and HFA227ea, apafurane. Norflurane is a gas at normal temperature (boiling point is minus 26.5°C) and filling the aluminium inhaler with liquid propellant has to be under high pressure in a totally sealed system; the metering valve delivering each puff was originally designed for dispensing perfume.⁵

Inhaled salbutamol and norflurane propellant from an MDI via a volumatic spacer is warmed in the spacer, is inhaled, deposited and absorbed through mucosa in the oral cavity, pharynx, trachea, and bronchii; jet nebulization through a mask is also absorbed in nasal passages and in both cases is swallowed and absorbed from the gut. Inhaled drugs cross the upper airway epithelium into the vasculature and when in the bronchii are thought to cross the airway lining fluid (a thick mucous layer and a periciliary layer of low viscosity containing water and solutes in which there are embedded layers of cilia) and then through the epithelium into helical bands of bronchial smooth muscle to reach the plentiful β_2 adrenergic receptors.⁶

Small and large salbutamol MDIs are available, smaller ones produce 7 ml of propellant and drug, larger ones 16 ml, 99% is propellant and this volume will exert a partial pressure according to Dalton's law and will aid delivery of drug to the lungs.

Lung deposition of radioactive-labelled HFA-134a beclomethasone (HFA-BDP) was 53% compared with 4% for labelled CFC beclomethasone (CFC-BPD) in healthy volunteers, the particle size of HFA-BDP was 0.9 μm and for CFC-BPD was 3.5 μm . This was thought to be the reason for better deposition of HFA-BPD further down the tracheo-bronchial tree; the partial pressure of HFA-134a exerted in the airways and a possible bronchodilator effect was not considered as another reason for better delivery and deposition.⁷

When using a spacer or chamber to increase the effectiveness of MDIs, 8–12 actuations are recommended in severe asthma as single puffs one at a time inhaled with five tidal breaths.⁴ Depending on the size of the spacer and if more than one puff is introduced before inhalation, the first part of inhalation will have a reduced oxygen percentage because of the exertion of a partial pressure effect. In severe asthma paediatricians will use up to 12 actuations into a spacer before a single inhalation by the patient.

Disposable jet or 'wet' nebulizers with oxygen as driving gas also rely on inhalation by an awake, co-operative patient and deliver salbutamol 2.5 mg in 2.5 ml, or 5 mg in 2.5 ml, diluted to 10 ml with normal saline delivered over 20 min; the addition of ipratropium bromide 500 μg will produce peak bronchodilator response.⁸ BTS recommends back-to-back nebulization of these two drugs over 20 min, that is, 3 in 1 h. Guidelines do not distinguish between the different nebulizers available and only give undiluted doses of nebulizer solutions; dilution is required in order to maintain nebulized solution production over a 20 min period (Table 1).

A blood level of 20–40 ng ml^{-1} of salbutamol can be achieved after 2 h of nebulizer therapy in children, and this is considered a level adequate to reverse bronchoconstriction.⁹

The use of disposable jet or wet nebulizer and their effectiveness is not evidence-based and there is a shortage of clinical trials and a lack of quality data.¹⁰ Studies of nebulizer performance show that only 5.7–12% of solutions reached the lungs in volunteers inhaling radioactive-labelled sodium chloride or albumin in saline^{11 12} and observations in one paper raised doubts as to whether therapeutic agents in aqueous solutions can be delivered by aerosol in significant amounts beyond the larynx. Reviews of delivery of radiolabelled drugs¹³ and performance of pressurized oxygen delivery nebulizers are researched *in vitro* or with healthy volunteers¹⁴ and may not apply to asthmatic patients.

Disposable jet nebulizers using oxygen as driving gas produce 0.5–10 μm median diameter liquid spheres which contain bronchodilating drugs in 0.9% normal saline and are thought to travel during inspiration in that state down the trachea to the bronchi and further. It is more likely that these drug spheres vaporize in the trachea and become part of the normal water humidification of inspired air and oxygen; thus, for example, nebulized salbutamol and ipratropium in sodium chloride will be deposited in the upper

Table 1 Performance of nebulizers (5 mg salbutamol in 2.5 ml)

Nebulizer	Oxygen flow (litre min^{-1})	Delivery rate (g or ml of saline)	Salbutamol delivery ($\mu\text{g min}^{-1}$)
Life Care®	7	0.34 ml min^{-1}	680
Intersurgical®	6	0.2 ml min^{-1}	400
	8	0.25 ml min^{-1}	500
Respironics®	6	0.37 g min^{-1}	740
	8	0.46 g min^{-1}	920

airways as they are not able to remain in water vapour. Saturated water vapour in the lower respiratory tract exerts a partial pressure of 6 kPa at 37°C and is a requirement for gas exchange in the alveoli.

During nebulization, the temperature of the solution in the nebulizer reservoir and the mist produced falls quickly from room temperature to 13°C and remains at this level over the usual 20 min nebulization period. The effect of this low temperature mist on the respiratory tract of asthmatics is not known, but the mist has to be warmed to 37°C in some part of the respiratory tract during inhalation. The bronchial circulation provides the heat and humidification of inspired air, and cooling of the respiratory epithelium causes vasodilatation and an increase in bronchial artery blood flow.

A number of different disposable oxygen-driven jet nebulizers are used in the UK and three different manufacturers' figures for rates of delivery of solutions are shown (Table 1).

Over a 7 min period, a Life Care® nebulizer will deliver 4690 µg of undiluted salbutamol (5 mg in 2.5 ml) to the mouth and nose and the nebulizer chamber will empty; over 5.4 min, a Respironics® nebulizer at 8 litre min⁻¹ oxygen delivers 4968 µg to the mouth and nose and the chamber will be empty. In order to maintain nebulization over a 20 min period, 7.5 ml of normal saline will need to be added to the 5 mg salbutamol in 2.5 ml saline solution in the Respironics® reservoir. A small tube can be left in the nebulizer chamber in order to keep it 'topped up'.

There is a constant production of nebulized mist and only a part of this will be inhaled during inspiration. If 5.7–12% reaches the lungs during inspiration, then the remaining therapeutic solution is absorbed in the upper respiratory passages or passes into the atmosphere during inspiration and more so during expiration. A useful check of the performance of a nebulizer is to see if clouds of mist produced are sucked in during inspiration and seen to increase during expiration.

Increasing the concentration of salbutamol from 2.5 to 7.5 mg in the same fluid volume of 5 ml from a nebulizer over 20 min showed no advantage of the higher dose in a study of 160 adult acute asthmatics; no details of the nebulizer were given nor an explanation for this result.¹⁵

Magnesium sulphate can be nebulized using 125 mg–500 mg, 2.5–5 ml in a nebulizer chamber. There is no mention of use of nebulized lidocaine in any asthma guidelines.

When clinical and pathological features of acute severe asthma are taken into account, pressurized inhaler or nebulized delivery of any appreciable drug dose to bronchial muscle must be in doubt. The time taken to set up a nebulizer by nursing or medical staff and the BTS requirements of back-to-back nebulization over 1 h create delay and further build up of oedema and mucus plugs. Acute asthmatics are anxious, sitting up, use accessory respiratory muscles, have hyper-inflated chests, and (especially children) do not take kindly to tight-fitting face masks. As clinical condition deteriorates, they are unable to speak, auscultation of the chest reveals no breath sounds, arterial carbon dioxide levels will increase as the patient becomes exhausted, consciousness is altered and then lost.

Inspiratory and expiratory volumes at this stage of the disease have never been measured. Pressures below the closed vocal cords, and volumes passing through the vocal cords to produce speech can be used as an estimate. A sub-glottic pressure of 8 cm H₂O before cord opening and a time of 100–250 ms per word is needed for speech.¹⁶ Patients with a cuffed tracheostomy speaking tube require an external oxygen flow of 2–8 litre min⁻¹ to enable them to speak; this gives a minimum flow through the cords for speech of 33 ml s⁻¹, an asthmatic who cannot speak may have a similar inspiratory volume. The inability to remove CO₂ also suggests very low respiratory volumes are moving in and out and thus inspiratory drug delivery in the face of airway resistance is futile.¹⁷

Air trapping, oedema of bronchial walls, and build up of mucous plugs are seen post-mortem in asthmatics¹⁸ and in life will also impede bronchodilatation via the inhaled route.

If the lower respiratory tract is receiving little or no metered dose or nebulized drugs, any absorption of bronchodilating drugs must be through vascular absorption from the upper airways and gut during long periods of metered doses or nebulization and therefore drug delivery to bronchial muscle is vascular. If reversal of bronchoconstriction is slow and there are no side-effects of salbutamol (tremor, tachycardia, and hypokalaemia), this suggests a low efficacy of inhaled drugs; during a long period of treatment, steroids have time to work and become effective at reducing bronchoconstriction.

Anaesthetic vapours

Anaesthetic inhalation agents have smooth muscle relaxing properties and can be delivered to spontaneous breathing asthmatic patients using tight-fitting anaesthetic face masks and low-resistance anaesthetic circuits through self-inflating reservoir bags, or continuous positive airway pressure devices using 100% oxygen, all of which may avoid intubation and ventilation¹⁹ by inducing bronchodilation before these procedures.²⁰ Patients may not accept and fight against a tightly held fully sealing anaesthetic face mask; they already feel suffocated and the addition of anaesthetic circuit resistance will add to this feeling. If inspiratory effort and volume is minimal, delivery to terminal bronchi and alveoli will be slow.

Halothane should not be used in the presence of hypercapnia but is still proposed in the Advanced Paediatric Life Support guidelines for anaesthetic induction before intubation of asthmatics.²¹ Isoflurane and desflurane are pungent and irritant and are reserved for ventilated patients; sevoflurane was found best in reducing airway resistance in non-asthmatics at an MAC of 1.1.²² The MDI propellant, HFA-134a, norflurane, a weak anaesthetic, is likely to have bronchodilating properties, but no studies have been performed to confirm this.

I.V. route

When the inhalation route fails, bronchodilatation may still be possible by using the i.v. route for magnesium sulphate,

salbutamol, terbutaline, epinephrine, and aminophylline, and may avoid intubation and ventilation, and reduce airway pressure during ventilation.

A comparison of three guidelines for the use of i.v. drugs is shown in Table 2.

I.V. treatment used in other specialities can guide drug dosage, speed of delivery, and occurrence of side-effects; β_2 stimulants and magnesium sulphate have a similar cellular mechanism of action on bronchial, uterine, vascular, bladder, and gut smooth muscle and are used i.v. for tocolysis in obstetrics. Magnesium sulphate is also used i.v. in eclampsia and severe pregnancy-induced hypertension and to treat atrial tachyarrhythmias.

Down to the terminal bronchii (1st–16th generation), the air passages and smooth muscle derive nutrition (and drug delivery) from the systemic bronchial circulation; from this point onwards, the small air passages and their muscles rely on the pulmonary circulation for their nutrition,²³ i.v. drugs will reach bronchial muscle from the pulmonary and the systemic circulation.

Magnesium sulphate

Magnesium has muscle relaxing properties in vascular and other smooth muscle and may decrease intracellular calcium. Magnesium sulphate-treated rabbit tracheal muscle strips were shown to relax when treated with constrictor agents, potassium chloride and acetyl choline. The conclusion was that magnesium inhibits calcium influx by blocking the voltage-dependent calcium channels.²⁴

Like salbutamol, magnesium is an activator of adenylyl cyclase, the enzyme involved in the synthesis of cyclic AMP and this inhibits calcium entry into cells.

I.V. magnesium sulphate appears to be safe and beneficial in patients who present with acute severe asthma.²⁵ BTS asks for senior advice to be sought before using 1.2–2 g over 20 min i.v. in adults, with no explanation of dosage or why a 20 min delivery time was chosen. A dose of 40 mg kg⁻¹ i.v. over 20 min is suggested in children.²⁶

An audit of i.v. magnesium sulphate use in the UK showed that 93% of 180 emergency departments use it in patients with acute severe and life-threatening asthma with most stating that they would give the drug if there was no response to repeated nebulization.²⁷

Speed of delivery of i.v. MgSO₄ in non-asthmatic patients can be fast and safe. In the great majority of cases of eclampsia, 4 g i.v. no faster than 1 g min⁻¹ and followed immediately by 10 g i.m., promptly arrested seizures and the patients were oriented and without profound central nervous system depression.²⁸ Acute effects of magnesium 4 g i.v. over 15 min followed by 1.5 g h⁻¹ in severe pregnancy-induced hypertension showed a transient hypotensive effect on mean arterial pressure.²⁹ In a study of six hypertensive and four normotensive male and female volunteers, magnesium sulphate was administered through a central venous catheter in a dose of 4 g given over 10 min.

Cutaneous warmth was felt, hypertensives had a transient decrease in mean arterial pressure, and normotensives had no appreciable change. Average total peripheral resistance decreased 23% in normotensives and 32% in hypertensives.³⁰ Fifteen adults presenting with newly recognized atrial fibrillation and ventricular rate of more than 99 bpm were given 2 g of i.v. MgSO₄ over 1 min followed by a continuous infusion of 1 g h⁻¹. Tingling, warmth, or flushing was reported; no significant decrease in arterial pressure occurred; ventricular rate decreased by an average of 16 (7%) within 5 min of the MgSO₄ bolus.³¹

For tocolysis, a bolus of 4 g MgSO₄ is followed by 2 g h⁻¹,³² but a combination of an MgSO₄ infusion, with an infusion of the β_2 agonist ritodrine hoping for a synergistic effect in tocolysis, caused an unacceptable increase in serious side-effects and did not improve efficacy. The prominent side-effect in 11 out of 24 patients after some days of infusion was chest pressure and pain and ST segment depression consistent with myocardial ischaemia. Fluid intake had been strictly controlled, the mechanism of the ischaemia was unexplained,³³ and a rebound effect of increased calcium levels may account for these effects.

MgSO₄ increases atrial conduction time and refractory-ness³⁴ in myocardial cells inhibiting calcium influx and blocking outward movement of potassium through ion channels in heart cells.³⁵

This cellular action fits an observation in one unconscious asthmatic patient in whom prior i.v. MgSO₄ prevented an expected β_1 tachycardia from a large bolus dose of i.v. salbutamol;³⁶ this was confirmed in a volunteer and then in a further five cases, with i.v. epinephrine tachycardia also avoided.³⁷

I.V. β_2 agonists, leukotriene receptor agonists, aminophylline, steroids, and epinephrine

In the USA, it is believed that there is no proven advantage of systemic (i.v. epinephrine, terbutaline, and salbutamol) over aerosol therapy in asthma,³ and a large meta-analysis could find no benefit of systemic therapy in the papers reviewed.³⁸ The i.v. route for salbutamol in asthma is advocated by the Canadian Medical Association only if the response to nebulization is poor, the patient is coughing excessively, is moribund, or becomes so despite inhalation therapy.³⁹

I.v. lidocaine is not mentioned at all in asthma guidelines.

The difficulty in comparing nebulization with i.v. delivery is illustrated by examination of contrasting results of two clinical research papers. Both are cited as evidence of one or the other route being better for salbutamol delivery. In the first paper, two 5 mg salbutamol nebulizations over 60 min were compared with 500 μ g of i.v. salbutamol over 60 min in a double-blind multicentre randomized trial of adult patients with acute asthma who had an average arterial CO₂ of 51 $\pm$ (8) mm Hg. Nebulized salbutamol had already been given to both groups (14 and 19 mean nebulizations,

Table 2 Comparison of guidelines for i.v. drugs in acute severe asthma. *They suggest nevertheless; child; terbutaline 0.01 mg kg⁻¹ every 20 min for three doses. Epinephrine 0.01 mg kg⁻¹ up to 0.3–0.5 mg every 20 min for three doses. Adult; terbutaline 0.25 mg every 20 min for 3 doses. Epinephrine 0.3–0.5 mg every 20 min for three doses

Guidelines	I.V. salbutamol		I.V. aminophylline		I.V. magnesium	
	Child	Adult	Child	Adult	Child	Adult
Australian 2006	15 µg kg ⁻¹ Over 10 min	250 µg Over 1 min	Only in ICU 10 mg kg ⁻¹	6 mg kg ⁻¹	40 mg kg ⁻¹ Over 20 min	2 g Over 20 min
USA NIH 2007	No proof of efficacy* (see above)	ditto	Not recommended	ditto	25–75 mg kg ⁻¹ No delivery time	2 g No delivery time, life threat, >1 h ICU
UK BTS 2012	15 µg kg ⁻¹ Over 10 min	Not mentioned	No proof of efficacy	Give after consultation	After senior consultation	1.2–2 g Over 20 min

respectively), which created salbutamol plasma levels of 2.9 and 3.6 ng ml⁻¹. After the additional nebulized or i.v. treatment, levels increased to 4.7 in nebulized and 5.9 ng ml⁻¹ i.v.; these are not high blood levels and the dose of 500 µg infused over 1 h is very small. The duration of the asthma attack before admission was 14 h in both groups, which suggests less than acute episodes of asthma. Results showed greater improvement in the nebulized group, potassium fall was more significant in the i.v. group, and tachycardia differences were not significant.⁴⁰

In the second paper, paediatric asthma cases already treated with salbutamol nebulization were then randomized to either receive further nebulization or be given i.v. salbutamol of 15 µg kg⁻¹ over 10 min in a blinded study; improvement of asthma was better and a reduced hospital stay occurred in the i.v. group.⁴¹ The use of 15 µg kg⁻¹ over 10 min is advocated in paediatric but not adult BTS guidelines and requires an infusion pump; an alternative is to deliver 5 µg kg⁻¹ boluses of salbutamol diluted from an ampoule containing 500 µg ml⁻¹; doses which are repeated.⁴² To prevent return of bronchoconstriction in children, a continuous salbutamol infusion of 5 µg kg⁻¹ min⁻¹ for 2 h in children with severe asthma who are clinically stable and on maximal medical therapy is considered safe.⁴³

A tachycardia from β1 effects is more likely after i.v. salbutamol in paediatric patients, and heart rate may increase to 200 beats min⁻¹;⁴⁴ tocolysis using the β2 agonist ritodrine creates a tachycardia and the British National Formulary recommends a dose reduction when a heart rate of 140 is reached.⁴⁵

Cellular cysteinyl leukotrienes cause bronchoconstriction (100–1000 times more potent than histamine), bronchial smooth muscle hyperresponsiveness, vascular permeability, and mucus formation. These interact with a specific receptor which is blocked by antagonists such as montelukast.⁴⁶ In a randomized trial, an i.v. leukotriene receptor antagonist, montelukast, given to moderate to severe asthmatics demonstrated a significant improvement in pulmonary function within 10 min of administration.⁴⁷

Methyl xanthines are not recommended in USA guidelines, but BTS guidelines state that i.v. aminophylline has a place in

acute severe asthma after consultation with senior medical staff and if there is little response to other treatment (which does not include i.v. salbutamol in adults); a loading dose of 5 mg kg⁻¹ over 20 min is followed by 1 mg kg⁻¹ h⁻¹. Using double the BTS loading dose caused troublesome vomiting⁴⁸ and too rapid infusion may result in seizures, severe vomiting, and fatal cardiac arrhythmias. MgSO₄ i.v. has anti-convulsant and anti-arrhythmic actions and may reduce some of these side-effects.

Steroids in doses of 200 mg i.v. hydrocortisone 6 hourly in adults and 4 mg kg⁻¹ repeated 4 hourly in children will take some hours to exert the maximum effect; i.v. and subcutaneous epinephrine may further increase bronchodilation, and an NIH (USA) adult i.v. dose is 0.3–0.5 mg every 20 min for 3 doses (Table 2).

Recognizing the reversal of bronchoconstriction requires the treating physician to remain with the patient and watch for clinical improvement in breathing, there is no reason to stop the delivery of nebulized drugs when using the i.v. route for bronchodilators; disappearance of nebulized clouds during inspiration and cloud increase on expiration are signs of improvement. Commencement of coughing and expelling of mucous plugs, return of audible wheeze or its reduction, less use of accessory muscles, improvement of consciousness, return of speech, and arterial blood CO₂ reduction are also signs of improvement.

Positive pressure ventilation (non-invasive and invasive)

Positive pressure ventilation when required does not reverse bronchoconstriction, it can be delivered non-invasively via a tight-fitting anaesthetic face mask⁴⁹ or through a tracheal tube, the insertion of which may itself provoke further bronchoconstriction. Ventilating the lungs of a severe asthmatic will push inhaled gas through oedematous and mucus blocked airways, exhalation will take a long time, and if not possible, will lead to distension of terminal bronchi and alveoli creating pneumothoraces and other barotrauma.

Propofol and ketamine are safe induction agents for tracheal intubation; ketamine will maintain arterial pressure and is a more potent bronchodilator than propofol in methacholine-provoked asthma in sheep.^{50 51} Succinylcholine will raise potassium, which is helpful if there is hypokalaemia after delivery of β_2 drugs, but succinylcholine may release histamine; rocuronium is safe. A reduction in the size of the hyperinflated asthmatic chest has been proposed by chest compression,⁵² and there are case reports of benefit of chest compression during respiratory arrest in asthmatics in the emergency department.⁵³

Ventilation should be slow allowing permissive hypercapnia and a long expiratory pause. Bronchial plugs are difficult to remove without a spontaneous cough and air trapping behind the plugs leads to bronchial and alveolar distension, which may be followed by their rupture creating barotrauma. Reviews of ventilation in asthma attest to its dangers.^{1 54} β_2 drugs from metered dose inhaler cartridges inserted into the breathing circuit⁵⁵ or nebulized drugs can be delivered via the tracheal tube, inhalation anaesthetic agents by vaporizers on anaesthetic machines, or by special equipment able to deliver inhalation agents through intensive care ventilators.⁵⁶ Weaning from ventilation and extubation requires the elimination of bronchoconstriction and extubation may itself provoke bronchospasm.

Discussion

In the UK, 4.3 million adults and 1.1 million children have asthma, 1204 deaths from asthma occurred in 2008, 29 deaths were of children under 14 yr; 90% of these deaths are preventable.⁵⁷ Two-thirds of deaths probably occur out of hospital and sudden death from asthma can occur over a very short period of time.⁵⁸ This equates to a death rate of 2 per 100 000 of the UK population; the death rate in pregnancy is 0.22 per 100 000 pregnancies,⁵⁹ a lower rate because of the protective effect of raised cortisol levels and other changes.⁶⁰

An audit of 65 381 hospital admissions for asthma in the USA showed a 5% incidence in tracheal intubation and ventilation and 0.5% mortality; the intubated and ventilated patients had a higher death rate.⁶¹

Precipitating factors for asthma attacks are viral infections, non-compliance with treatment, and climatic changes; thunderstorms can raise aerosols of mostly fungal spores provoking bronchospasm.⁶²

Using metered dose or nebulized β_2 agonists for asthma treatment relies on an assumption that delivery to, and absorption from, the trachea and bronchi is efficient. This cannot be guaranteed especially when respiratory incursion and excursion is severely limited. Bronchodilators with β_2 effects delivered i.v. are safe; fears of dangerous side-effects may prevent the use of the i.v. route, but the β_1 side-effect of tachycardia is attenuated by prior magnesium sulphate and potassium falls are predictable and treatable.

Side-effects in self-poisoning with oral salbutamol or terbutaline showed a β_1 effect of tachycardia; β_2 effects

caused tremor in some, a low potassium ranging from 2.0 to 4.2 mmol litre⁻¹, and hyperglycaemia with maximum plasma drug concentrations ranging from 41 to 88 ng ml⁻¹. These side-effects were much less serious than those seen after theophylline overdose with comparably elevated plasma concentrations.⁶³

Lactic acidosis in arterial blood samples during nebulized and i.v. salbutamol treatment of asthmatics has been reported; mechanisms are unknown, but the acidosis reverses quickly with a reduction in the rate of salbutamol delivery.⁶⁴

In one series of case reports and a review, physicians in the USA treating pregnant severe asthmatics moved directly from nebulization failure to intubation and ventilation without recourse to i.v. bronchodilating drugs. One patient was given subcutaneous terbutaline. Ventilation of the lungs used a low respiratory rate, a volume assist-control mode, and inhaled β_2 agonists; patients were sedated with propofol and fentanyl and some received neuromuscular blocking agents.⁶⁵

Methods of bronchodilation have different approaches in different countries. In Australia and New Zealand, there have long been advocates of the i.v. route for salbutamol, even given by general practitioners in areas without swift access to medical centres. Children with severe asthma treated in Westmead Children's Hospital, Sydney, are rarely intubated and ventilated.⁴³

Information on drug use, effect, experience, and research in other specialities guides us in management of asthmatics, for instance, ergometrine constricts the smooth muscle of the uterus and blood vessels, it has provoked bronchoconstriction in pregnant asthmatics and in two cases probably contributed to their deaths.^{66 67}

Anaesthetists and intensivists are well versed in delivery of i.v. drugs, their immediate effects, and are able to deal with the results; those who have used the i.v. route for asthma drugs (and the patients who have received them) can attest to the safety, efficacy, and immediate reversal of bronchoconstriction. Research proving an advantage of the i.v. route for asthma drugs (or heliox⁶⁸ to deliver anaesthetic vapour) using blinded controlled studies may be impossible in life-threatening asthma; anecdotal case reports, especially about managing severe asthma, should be recognized as opinions and experience and may be defined as category IV evidence, the strongest evidence available to help manage infrequent emergency situations.⁶⁹

Future research to determine the dose of i.v. magnesium and the timing before i.v. salbutamol to protect the atria from β_1 -induced tachycardia can be studied in volunteers; the possible bronchodilating effect of norflurane needs investigating, and the use of heliox to drive nebulizers⁷⁰ or to deliver anaesthetic vapours.

The misery and distress of asthmatics during prolonged futile MDI and nebulizer therapy can be avoided by using the i.v. route for magnesium and salbutamol, if ventilation is unavoidable, i.v. drugs will reduce morbidity and mortality.

Declaration of interest

None declared.

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Appendix: Treatment of an acute severe asthmatic; deteriorating, unconscious, or moribund

Transfer to resuscitation area, gain i.v. access.

100% oxygen using anaesthetic circuit (Mapleson A) or continue mask nebulization at 8 litre min⁻¹ oxygen flow or self-inflating bag and mask attached to common gas outlet giving 100% oxygen, attempt ventilation if moribund.

Add sevoflurane (optional).

I.V. hydrocortisone 4 mg kg⁻¹ (if not already given).

I.V. magnesium sulphate up to 40 mg kg⁻¹ over 5–10 min or less (1 g = 4 mmol).

I.V. salbutamol 5 µg kg⁻¹ over 2–3 min and repeated, or; i.v. salbutamol 15 µg kg⁻¹ over 10 min and repeated.

If no improvement, rapid sequence induction using i.v. ketamine 2 mg kg⁻¹ or propofol 1–2 mg kg⁻¹ followed by i.v. succinylcholine 1–2 mg kg⁻¹ (will raise potassium).

Intubate trachea (not right main bronchus), compress the chest to reduce hyperinflation, ventilate to oxygenate with permissive hypercapnia, add sevoflurane and/or i.v. salbutamol up to 5 µg kg⁻¹ min⁻¹.

Prepare for pneumothorax, pneumomediastinum, and pneumoperitoneum.

NB. Paediatric self-inflating bags have a pressure relief blow-off valve, not adult ones.

Handling editor: R. P. Mahajan