

RESPIRATION AND THE AIRWAY

Emergency treatment of status asthmaticus with enoximone

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Editor's key points

- Enoximone is a phosphodiesterase III inhibitor, primarily used in treatment of heart failure.
- The author presents a case report of eight patients with status asthmaticus refractory to treatment.
- Enoximone was effective in all these patients in reversing bronchospasm.
- Enoximone may have a role in refractory status asthmaticus in preventing tracheal intubation and mechanical ventilation.

This report describes the treatment of eight patients with status asthmaticus, six of whom were already maximally treated. They were consequently treated with enoximone, a selective phosphodiesterase III inhibitor, in their refractory phase. Bronchodilatation in these patients was immediate. No side-effects were observed. Enoximone appears to be a valuable addition to the treatment of status asthmaticus. I.V. administration bypasses inhalation incapability in severe asthma. It is likely to reduce or altogether prevent the need for resorting to secondary or tertiary high-tech therapy such as mechanical ventilation or anaesthetics, thus avoiding complications, as well as for transfers to specialized intensive care units. Not only do these aspects enable substantial cost savings, but they also may spare the patient a lot of anguish and a prolonged recovery.

Keywords: asthma; enoximone; intensive care; respiratory factors

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Asthma is a chronic disease of the airways, characterized by variable and recurring symptoms, airflow obstruction, bronchial hyper responsiveness (bronchospasm), and inflammation. In severe exacerbations intensive care admission may be necessary. Pharmacological treatment includes beta-2-mimetics, anticholinergic agents, magnesium sulphate, steroids, and sometimes aminophylline. When these drugs have no effect, intubation is often necessary, sometimes followed by i.v. administration of ketamine or S-ketamine. However, in extreme bronchoconstriction, all of these are of little or no avail.

In the past 25 yr literature has hinted at the therapeutic potential of phosphodiesterase (PDE) III inhibitors in asthma;^{1–4} however, today none of these drugs is available for this indication. This paper describes the use of the PDE III-inhibitor enoximone in status asthmaticus during the period 2008–2013.

Enoximone is a selective PDE III inhibitor used for treatment of heart failure; it increases cyclic AMP and ionized calcium in the myocyte, resulting in increased myocardial contractility. In vascular wall smooth muscle cells, enoximone causes an increase in cyclic adenosine mono phosphate (cAMP) and in cyclic guanosine mono phosphate (cGMP), resulting in relaxation and subsequent vasodilatation.^{5,6} In bronchial smooth muscle cells, it causes bronchodilatation.^{1,2,7}

The author's many years of experience with enoximone in intensive care and in the treatment of heart failure, combined with logic, led to the assumption that the dilatory effects of this drug might be beneficial in severe asthma.

Case reports

The first patient was a 34-yr-old female with a known history of severe asthma and atopic eczema; her sister died in an asthma attack some years earlier. She was presented at the Emergency Department in a status asthmaticus. She was brought in by ambulance suffering from extreme dyspnoea, flailing with arms and legs in utter panic. On examination, she showed tachycardia, tachypnoea, inspiratory and expiratory wheeze, and prolonged expiration. She had no fever. Shortly after arrival she suffered a respiratory arrest, seizures, and urinary incontinence. She was immediately intubated. Her capillary blood gas in the emergency room was as follows: pH 7.07; P_{aCO_2} 12.2 kPa; P_{O_2} 4.8 kPa; SO_2 46%. Under the diagnosis of status asthmaticus, she was transferred to the intensive care unit (ICU), where she received salbutamol/ipratropiumbromide by nebulizer, steroids, ketanest, and aminophylline i.v., without any substantial effect. Mechanical ventilation was nearly impossible, yielding a minute volume of maximally 2.5 litres, accompanied by persistent blocking of the ventilator. The first arterial blood gas in ICU revealed the following values: pH 7.08; P_{aCO_2} 10.6 kPa; P_{O_2} 19.0 kPa; and SO_2 98%. As a last resort, a rapid bolus of 100 mg enoximone was given i.v. Within 2 min, the minute volume increased to 14 litres. One hour later, the blood gases had improved to pH 7.24; P_{aCO_2} 7.3 kPa; P_{O_2} 22.2 kPa; and SO_2 99%. Treatment was continued with an infusion of 8 mg enoximone per hour. After 5 days she

was weaned from the ventilator and was successfully detubed.

Subsequently, all presented status asthmaticus patients were treated with enoximone.

Between 2008 and 2013, seven more patients were presented to the author for mechanical ventilation in three different hospitals. All of them were in their refractory phase. Of the total of eight patients, six could be classified as near-fatal asthma because of their respiratory arrest, increased P_{aCO_2} , or both; two could be classified as life-threatening asthma according to the British Guideline on the Management of Asthma, 2008 revised January 2012 (Table 1).⁸

All patients received enoximone i.v.; the dose depended on their level of consciousness, their ability to speak, or both. Patients 2, 3, 6, and 7 allowed titration (Table 2) rather than a bolus; their dyspnoea resolved within seconds. Patients 4, 5, and 8 were extremely dyspneic (see Table 1 for their high P_{aCO_2} and low pH) and Patients 4 and 5 received a large bolus of 100 mg. Patient 4 panicked during administration and therefore was intubated; within 5 min, he received a second bolus of 100 mg. He could be weaned from the ventilator within 24 h. Patient 5 was extremely hypercapnic and acidotic, so he also received a second bolus of 100 mg within 5 min. His dyspnoea symptoms resolved within 15 min. With Patient 8 the time to return of sufficient breathing was actually measured; it was 20 s after the enoximone injection.

All patients received salbutamol, aminophylline pre-ICU, or both, ordered by the pulmonologist. Emergency room or ICU

treatment contained immediate administration of enoximone; after the resolution of the acute asthma attack, the patients received standard asthma treatment, including salbutamol, ipratropium, and steroids.

Results

After administration of enoximone, the restoration of spontaneous sufficient breathing occurred within seconds in all patients, regardless of the severity of the asthma. This is one circulation time from arm to lungs. Dyspnoea resolved within 20–30 min, the time to recuperate from hypercapnia. No rebound was seen during hospital stay.

The enoximone was very well tolerated without cardiovascular side-effects.

Follow-up

The first patient was admitted again for an asthma exacerbation 6 months later to the pulmonary department for 6 days. The pulmonologist saw no need to consult the intensivist; the patient received the usual treatment (no enoximone) and has been treated on an outpatient basis ever since.

Patients 2–4, and 6 have been treated on an outpatient basis since their first admittance. Patient 7 also suffers from liver cirrhosis and has been readmitted to the hospital several times.

Patient 5 has moved abroad, providing no further data. Patient 8 was only recently discharged from the hospital.

Table 1 Patient characteristics. *Asthma severity according to the British Guideline on the Management of Asthma.⁸ m, male; f, female

No.	Age-sex	Asthma severity*	pH	P_{aCO_2} (kPa)	P_{aO_2} (kPa)	Heart rate ≥ 110 (min ⁻¹)	Exhaustion	Respiratory arrest
1	34—f	V	7.07	12.2	4.8	x	x	x
2	66—m	V	7.35	7.0	8.6	—	x	—
3	74—m	IV	7.46	4.7	10.5	x	x	—
4	67—m	V	7.16	9.2	10.2	x	x	—
5	16—m	V	6.98	15.0	8.4	x	x	x
6	62—m	IV	7.29	9.7	10.9	x	x	—
7	55—f	V	7.22	9.1	13.5	x	x	—
8	60—f	V	7.10	13.8	11.8	x	x	x

Table 2 Treatment received by different patients. *Received continuous i.v. enoximone (8 mg h⁻¹) during ICU stay

No.	Steroids	Theophylline	MgSO ₄	Salbutamol nebulization	Ketamine	Enoximone dose(s) (mg)	Mechanical ventilation (days)
1	x	x	x	x	x	100*	5
2	x	x	—	x	—	50 (2 × 25)*	—
3	x	x	—	—	—	30 (3 × 10)	—
4	x	x	—	—	—	200 (2 × 100)*	1
5	x	—	—	—	—	200 (2 × 100)*	—
6	x	—	x	x	—	40 (4 × 10)	—
7	x	—	x	x	—	50 (2 × 25)	—
8	x	—	x	x	—	60 (35 + 25)	—

Discussion

Worldwide, between 235 and 300 million people are affected by asthma and ~250 000 people die from the disease per year. It is the most common chronic disease among children. Asthma occurs in all countries, regardless of the level of development. More than 80% of asthma deaths occur in low and lower-middle income countries.^{9 10} Asthma is often under-diagnosed and under-treated, creating a substantial burden to individuals, families, and health services, and possibly restricting individuals' activities for a lifetime. It is essential to make medication more effective, affordable, and available, relieving the physical and financial claim asthma poses on its sufferers and on health authorities.

In the past 10 yr, the increase in asthma cases in the USA alone has been 48%. In the UK in 2012 ~80 000 emergency hospital admissions and 1200 deaths were reported for asthma. No improvement in treatment for a decade has cost the NHS 100 million pounds.⁹

Dutch ICUs participating in the Dutch NICE (Netherlands' Intensive Care Evaluation) quality registry evaluated their performance. Over 2008–2010, 330 severe asthma patients aged ≥ 16 yr were admitted to these ICUs. Of these, 190 (58%) required mechanical ventilation with a mean of 3.1 days. The hospital mortality was 31 (9%).

While most asthma can be controlled with medication, an estimated 5–10% of the USA asthma population (and this is believed to apply to the world population as well) is considered to have the most severe persistent form of the disease that does not respond well to treatment. These people are likely to have more attacks and are more at risk of a fatal attack.¹¹

Given these data, the treatment of status asthmaticus in refractory bronchial asthma presents a challenge to the physician and the health services. A simple and adequate way to reduce distress and costs would have great merit.

Treatment aims primarily at preventing intubation and mechanical ventilation. As mentioned above, in cases of severe bronchoconstriction, pharmacological treatment is often of little or no avail. The benefit of theophylline is challenged.^{8 12 13} It is an α -selective phosphodiesterase inhibitor with a narrow therapeutic range and may cause seizures (as was the case with Patient 1) and arrhythmias. It was abandoned in favour of the more potent aerosolized beta-2-mimetics. Its minor bronchodilatory effects are mainly attributable to adenosine 1 and adenosine 2 agonist activity. Its usefulness in status asthmaticus was never sufficiently established. Currently, it has a revival in steroid resistant asthma.¹⁴

At present, two selective phosphodiesterase III inhibitors are commercially available: enoximone and milrinone.

Enoximone is an imidazole with a $T_{1/2}$ of 4 h and milrinone a bipyridine with a $T_{1/2}$ of 2 h.¹⁵ With both, inhibition of cAMP and cGMP breakdown in bronchial smooth muscle cells leads to bronchodilatation. Both are said to be calcium sensitizers as well, but this is not extensively documented. Milrinone is also an agonist of the Ryanodine Receptor (RyR) of the myocardial Sarco Endoplasmic Reticulum (SER), triggering the myocardial calcium release, both systolic and diastolic, and may somewhat compromise diastolic relaxation. Excessive triggering of the RyR may lead to cardiac arrest by massive calcium release from the myocardial SER.¹⁶ Both enoximone and milrinone are vasodilators. However, the vasodilatory properties of milrinone may cause severe hypotension, restricting the use in acute medicine (Table 3).¹⁷

The use of beta-2-mimetic drugs is limited because of tachycardia. In advanced cases of bronchoconstriction, nebulization fails because the inhaled drugs never reach the small bronchioli. Mechanical ventilation may ultimately be necessary but may introduce a host of complications, such as ventilator-related infections and mechanical lung tissue damage. Ventilatory treatment for refractory asthma can go as far as inhalation anaesthetics such as sevoflurane and extracorporeal carbon dioxide extraction and oxygenation [by extra corporeal membrane oxygenator (ECMO)].^{18 19}

When intubation cannot be avoided, it usually takes 3–5 days before the bronchoconstriction becomes less severe and weaning from the ventilator can be initiated.

Most asthma patients are admitted to community hospitals, with no proper equipment to treat severe deterioration; transfer to a secondary ICU (in specially equipped ambulance cars) is often necessary. These transfers are not only life threatening, as they obviously delay treatment, but also increase costs. With enoximone treatment no transfers are required; it also enables shorter hospital and ICU stays and a reduced need for mechanical ventilation, cutting costs, and risks considerably.

Treatment with enoximone worked instantaneously, regardless of the severity of the asthma or the dosage. All non-ventilated patients mentioned without prompting that the resolution of their asthma symptoms was immediate. The onset of action was within seconds of the start of injection, suggesting an effect at first passage through the lungs, resolving bronchospasm. This implies that the result very likely is not attributable to the cardiovascular effects of enoximone (as these take 10–30 min),²⁰ but to its bronchodilatory properties.

Literature provides several cases with adverse effect and fatal outcome in the use of enoximone for the chronic treatment of severe heart failure.^{21–23} A reason might be that enoximone in heart failure was given in exceedingly high doses up to

Table 3 Properties of the phosphodiesterase (PDE) inhibitors. *Ratio of positive inotropic ED₂₀ (PI) to peripheral dilatation ED₂₀ (PV)¹⁷

	PDE-inhibition	RyR-agonist	Clearance	Rel. PDE-inhibition capacity	Ratio PI/PV*	T _{1/2} -elimination (h)
Theophylline	Aselect	–	Liver	1	?	?
Enoximone	III	–	Liver/kidney	70	0.58	4
Milrinone	III	+	Kidney	200	0.05	2

2400 mg daily; doses like that are extremely likely to cause severe side-effects. In the patients described in this paper, the doses used were considerably lower and the duration of administration was substantially shorter. The early research in pulmonary use of enoximone has been abandoned, and since the late 1990s, the sparse research into PDE III inhibitors for pulmonary uses has not led to the use of any of these drugs in the treatment of asthma. Keeping in mind the possible cardiovascular side-effects of enoximone, the better option, in asthma treatment, for administering the drug i.v. is probably to titrate. However, in extremely severe cases, there is no other option than a relatively large rapid bolus.

Several prospective studies are being prepared with the aim to unravel the reproducibility of the described effect and the way of action, *in vitro* and in animals and humans.

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Declaration of interest

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