ORIGINAL RESEARCH LETTER

Enoximone in status asthmaticus

To the Editor:

Bronchial asthma is a chronic disease affecting >300 million people worldwide [1]. The most severe disease manifestation is status asthmaticus, which can be unresponsive to medical therapy. Patients with severe status asthmaticus who require intubation and mechanical ventilation have mortality rates of up to 20% [2]. Airflow obstruction is often so severe that adequate decarboxylation and protective ventilation are not feasible, and extracorporeal membrane oxygenation (ECMO) support is nowadays an established treatment option as a bridge to recovery [3, 4].

In 2014, Beute [5] described a series of eight patients with status asthmaticus refractory to standard treatment in whom enoximone, a phosphodiesterase (PDE)-3 inhibitor, caused immediate bronchodilatation. To the best of our knowledge, these observations have not yet been confirmed by others. We here report a case of a patient with refractory status asthmaticus who showed rapid and sustained bronchodilation after intravenous administration of enoximone.

A 54-year-old female patient was transferred to our intensive care unit from another hospital with refractory status asthmaticus. The otherwise healthy patient had been diagnosed with mild allergic bronchial asthma for >10 years. Her symptoms were well controlled with formoterol as needed. The patient had been admitted to another hospital 1 day earlier with severe asthma symptoms refractory to treatment with high-dose systematic corticosteroids, magnesium, parenteral and inhaled β_2-agonists, an inhaled muscarinic receptor antagonist, and inhaled adrenaline. Intubation was required but mechanical ventilation proved almost impossible due to severe airflow obstruction. Upon arrival at our centre, arterial blood gas analysis showed a carbon dioxide tension of 144 mmHg and severe acidosis with a pH of 6.9 (minute ventilation volume of 1 L with a peak inspiratory pressure (P_{insp}) of 43 cmH_2O, a positive end-expiratory pressure (PEEP) of 8 cmH_2O and an inspiratory oxygen fraction (F_{IO_2}) of 100%). Venovenous ECMO was instituted immediately, which allowed for effective decarboxylation and protective ventilation (pressure controlled, F_{IO_2} 40%, P_{insp} 27 cmH_2O, PEEP 11 cmH_2O and respiratory rate 11 per min). The patient was sedated with isoflurane, ketamine and propofol. Antiobstructive treatment was continued with systemic corticosteroids, inhaled β_2-agonists and antimuscarinergic agents.

Over the next 3 days, the clinical situation was stable but severe airflow obstruction persisted, so we decided to try enoximone based on the aforementioned case series [5]. As this compound is no longer readily available, it took 24 h to deliver, during which time the patient's airflow obstruction had slightly improved but continued to be severe (figure 1). Enoximone was administered intravenously starting with a bolus infusion of 0.5 $mg \cdot kg^{-1}$ over 20 min followed by a constant infusion rate of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, based on the prescribing information and the previous experience reported by Beute [5]. Within 15 min after start of treatment, expiratory flow improved and the tidal volume increased from 470 to 561 mL (figure 1). P_{insp} was gradually decreased from 16 to 10 cmH_2O over the next 10 h. Besides an increase in heart rate by ~10 beats per min, no discernible side-effects were observed. Over the next 3 days, airflow obstruction resolved (figure 1) and enoximone was gradually weaned off over a period of 12 h. The ECMO was removed on the third day after enoximone was started and the patient was extubated a few hours later on the same day. Another 3 days later, the patient was transferred to a normal ward.

Enoximone was originally developed for the treatment of severe heart failure [6]. Because of its relatively short plasma half-life of ~60 min, the drug is usually administered *via* continuous parenteral infusion [7]. Enoximone acts as an inotrope by inhibiting PDE-3 activity and increasing intracellular cAMP

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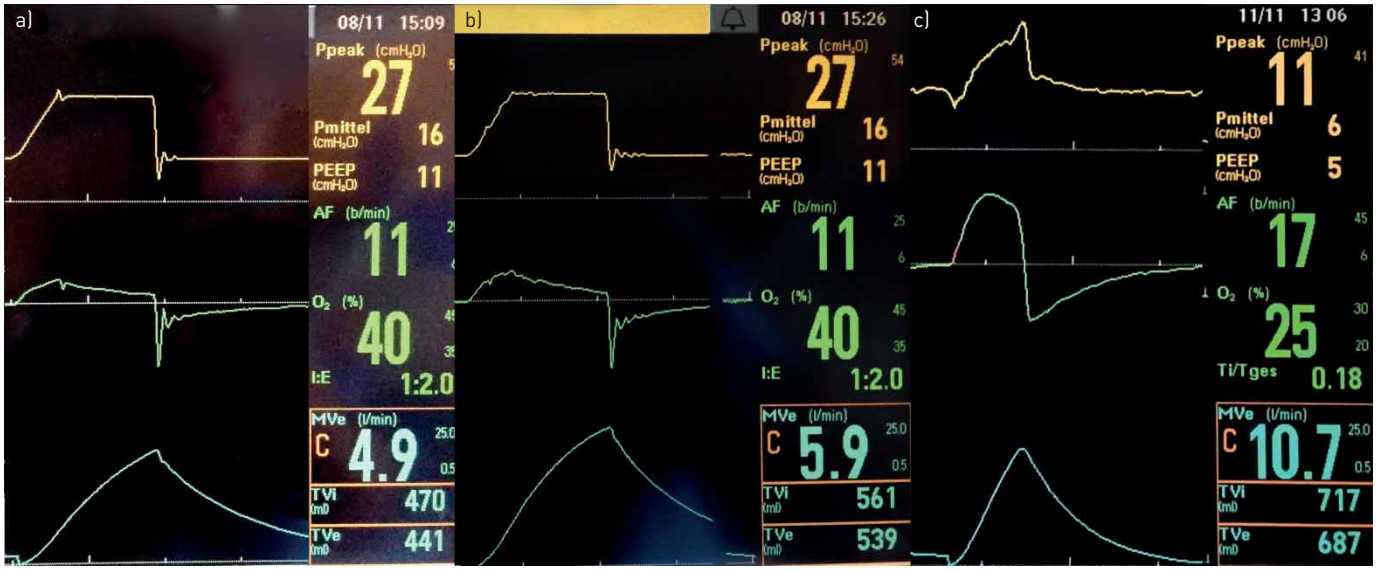

FIGURE 1 Screenshots from the ventilator. Pressure (top, yellow), flow (middle, green) and volume (bottom, blue) curves with corresponding ventilator settings and tidal volume measurements a) immediately before administration of enoximone, b) 15 min after enoximone had been started and c) 3 days later, immediately before extubation. Ppeak: peak inspiratory pressure; Pmittel: mean airway pressure; PEEP: positive end-expiratory pressure; AF: respiratory rate; O_2: inspiratory oxygen fraction; MVe: expiratory minute volume; TVi: inspiratory tidal volume; TVe: expiratory tidal volume.

concentrations in cardiac myocytes [7]. Increasing intracellular cAMP is also the main mechanism of β_2-agonists in patients with bronchial asthma [7]. As in our case, patients with status asthmaticus are usually unresponsive to β_2-agonists, at least partly due to receptor desensitisation [4]. In experimental models of allergic asthma, enoximone has bronchodilatory and anti-inflammatory effects, yielding a biological rationale for using this compound in patients with severe asthma [8].

Protective ventilation with the use of ECMO or extracorporeal carbon dioxide removal has become a mainstay in treating patients with severe status asthmaticus, and the majority of patients eventually recover [9]. In our patient, we saw the first signs of recovery at the time when we started enoximone, so we do not claim that this drug was lifesaving in our patient. Nevertheless, we feel that it is important to communicate this case, as the rapid and sustained response to enoximone suggests that this compound (and perhaps other PDE-3 inhibitors) may have a potential therapeutic role in patients with severe asthma. This hypothesis is supported by recent data on the use of inhaled PDE-3 inhibitors in patients with bronchial asthma [10]. Together, these findings warrant further exploration of the therapeutic potential of PDE-3 inhibitors in this patient population.

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