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## Withdrawal syndrome following midazolam infusion

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Sir: Acute benzodiazepine withdrawal syndrome is a well documented entity in psychiatry. We would like to report a case presenting with seizures and weaning difficulties following very long term midazolam infusion.

A 36-year-old woman ingested a 6 g amitriptyline overdose. She had no previous history of seizure and was chronically treated by amitriptyline and chlorazepam. She was found comatose with hypertonia, exaggerate deep tendon reflexes and twitching. Plasma amitriptyline concentration was 12.7  $\mu\text{mol/l}$  (therapeutic range: 0.3–1  $\mu\text{mol/l}$ ) on admission. A first electroencephalogram (EEG) allowed to rule out seizure changes. Mechanical ventilation was started immediately, as inhalation pneumonia was demonstrated, and midazolam and alfentanil were chosen for sedation. Midazolam was infused initially at a dose of 15 mg/h and alfentanil at 1 mg/h. On day 5, acute respiratory distress syndrome (ARDS) developed. Ventilation with high levels of positive end expiratory pressure was needed and the sedation was deepened. Midazolam was then infused at a rate of 20 mg/h for several days (Fig. 1). Finally, the resolution of the ARDS was obtained and the clinical course was favorable. The weaning from the ventilator started on day 21 and the administration of sedative drugs was decreased on day 22 and discontinued on day 33 (Fig. 1). It could be calculated that the patient had received a cumulative dose of 13440 mg midazolam during the ICU stay. Alfentanil had been given over a 11-day period (from day 1 to 11). On day 31, after midazolam infusion had been reduced from 10 to 2.5 mg/h, the patient complained from anxiety and insomnia and tremor was also noted. On day 33, about 6 h after midazolam withdrawal, extubation was considered but the patient was found agitated. Biological data revealed: pH 7.32,  $\text{PaO}_2$  11.2 kPa,  $\text{PaCO}_2$  8.10 kPa,  $\text{SaO}_2$  95%, blood glucose level: 5.8 mmol/l (4.45–6.10), calcium 2.34 mmol/l (2.30–2.60), phosphate

0.91 mmol/l (1.12–1.80), magnesium 1.64 mmol/l (0.74–0.98). Amitriptyline was no more detectable in plasma since day 22. The patient became unresponsive to verbal stimulation, with upward gaze deviation and left-sided myoclonic movements.

An EEG was performed at this time and displayed slow waves activity with paroxysmic elements predominating in the temporal and parietal areas. The injection of 1 mg clonazepam resulted in recovery of consciousness and return of the electroencephalographic trace within the normal range. Benzodiazepine withdrawal syndrome was suspected and it was decided to re-introduce midazolam (10 mg/h). Extubation was possible few hours later. Accidental discontinuation of midazolam 10 h later resulted in anxiety and tremor, without clinical evidence of epileptiform manifestations. However, seizures changes could still be found on the EEG. Clonazepam was chosen for its potent anticonvulsant properties and infused continuously at a daily dose of 3 mg; chlorazepate was given for insomnia. Further evolution was uneventful. An EEG performed 24 h later showed only a predominance of  $\beta$  waves. Cerebral com-

puted tomodensitometry failed to reveal any abnormality.

Benzodiazepine physical dependence is associated with the long-term use of both short and long-acting drugs. Some authors suggest that withdrawal could even be more severe and precocious with short-acting benzodiazepines with short half-lives than with long-acting with prolonged half-lives [1]. However, reports of withdrawal syndrome induced by an ultra short-acting benzodiazepine like midazolam appeared only recently [2, 3]. Boisse et al. demonstrated in an animal model that midazolam was able to induce severe physical dependence and withdrawal syndrome in rats. The duration and the severity of these withdrawal manifestations increased with chronic midazolam dose and duration of treatment [4]. In humans, withdrawal manifestations could also occur during the time of infusion with high doses midazolam, due to possible fluctuations in plasma concentrations. The patient may then present with agitation and it could erroneously lead to a further increase in midazolam prescription. The physicians who are prescribing long-term infusions of midazolam should be aware of these manifestations and

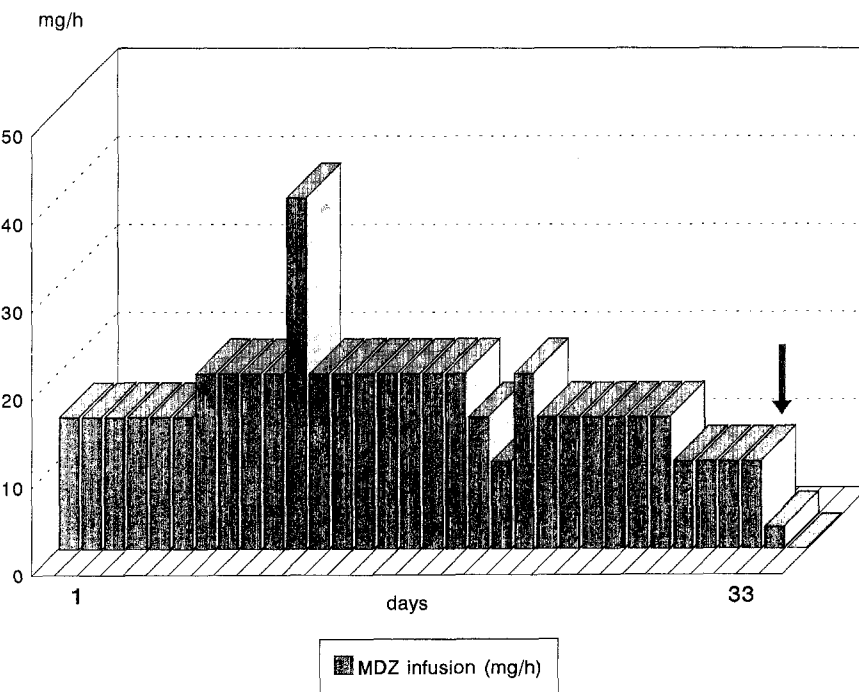


Fig. 1 Midazolam infusion cumulative dose during ICU-stay. The arrow indicates the onset of withdrawal manifestations

midazolam infusion should be reduced gradually.

The present case illustrates that sudden withdrawal of narcotic drugs is an important cause of new-onset seizures in ICU patients and should also be kept in mind in case of weaning difficulties [5].

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## External high-frequency ventilation in patients with respiratory failure (external ventilation)

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Sir: We present 3 cases in which external high-frequency ventilation (EHFV) was

applied using the Hayek oscillator (Flexco Medical Instruments, Oberengstringen, Switzerland) in patients with respiratory failure on mechanical ventilation. EHFV has several advantages: it does not require intubation, is quick and easy to apply, does not compromise cardiac output [1], and has physiotherapeutic effects that facilitate the removal of secretions [2]. The Hayek oscillator is a fully computerized, noninvasive respiratory, providing pulmonary ventilation by externally applied high-frequency oscillation. It consists of a flexible, light-weight cuirass, connected to a power unit, the oscillator, which creates cyclic pressure changes within the chest enclosure, around a negative baseline. The keyboard enables adjustment of frequency (up to 999 cycles/min). I/E ratio, and inspiratory and expiratory pressure.

### Case 1

A 65-year-old woman was admitted to the ICU with complete bilateral diaphragmatic paralysis after coronary artery bypass. She was placed on intermittent mandatory ventilation (IMV) for 36 days.

Tracheostomy was performed after 15 days of mechanical ventilation. EHFV was applied 16 h daily to facilitate weaning from mechanical ventilation. Frequency was initially 120 cycles/min, gradually decreasing to 50 cycles/min, each day. The I/E ratio was 1:1, inspiratory pressure (IP),  $-20$  cm H<sub>2</sub>O, and expiratory pressure (EP),  $7$  cm H<sub>2</sub>O. After 12 days of EHFV, the patient was weaned from the ventilator. Although she was discharged with tracheostomy, there was a significant improvement in diaphragmatic function.

### Case 2

A 71-year-old man was admitted to the ICU with acute exacerbation of chronic obstructive pulmonary disease (COPD) due to right lower lobar and pneumococcal sepsis. After intubation, control-mode ventilation (CMV) was implemented. Attempted weaning from ventilatory support using IMV ended prematurely with self-extubation after 13 days of mechanical ventilation. A decision was taken to ventilate the patient with EHFV. The Hayek Oscillator was used with an initial frequency of 120 cycles/min, gradually reduced to 25 cycles/min, an I/E ratio of 1:1, an IP of  $-22$  cm H<sub>2</sub>O, and an EP of  $10$  cm H<sub>2</sub>O, resulting in a significant improvement in the clinical state of the patient and a gradual improvement in arterial blood gases (ABG). Following EHFV, the patient expectorated a large amount of sputum. He was discharged 13 days after extubation.

### Case 3

A 39-year-old paraplegic man (following poliomyelitis contracted in childhood) was admitted to the ICU with acute respiratory failure due to pneumonia. He was intubated and ventilated with CMV and IMV for 14 days. It was impossible to wean the patient from the ventilator with conventional methods (SIMV, pressure support), therefore EHFV was implemented for 7 h starting with a frequency of 120 cycles/min gradually decreasing to 30 cycles/min, an I/E ratio of 1:1, an IP of  $-25$  cm H<sub>2</sub>O, and an EP of  $-8$  cm H<sub>2</sub>O.

The patient expelled a large amount of mucus through the endotracheal tube. After 4 days, he was able to breathe spontaneously, ventilation was discontinued, and extubation was performed.

EHFV was successfully applied in each of our 3 cases. Reventilation was achieved within seconds and the hazards of reintubation were eliminated. EHFV is an additional mode of mechanical ventilation in patients with respiratory failure. In our limited experience, it was virtually free from complications.

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