

## Case Report

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# Paradoxical Reaction to Hypnotics in Intensive Care Unit

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**Background:** Paradoxical reactions (PR) to benzodiazepines are well-known, but PR can also follow sedation by propofol, although this has been reported only in the context of operating room anesthesia. We report a rare case of paradoxical excitement induced by midazolam and propofol.

**Case presentation:** A 78-year-old patient presented with multiorgan failure secondary to infectious pneumopathy. During intensive care unit (ICU) stay, he experienced 2 episodes of ventilator-acquired pneumonia and 1 of acute kidney failure requiring renal replacement therapy. Throughout the stay, he showed restlessness, uncontrollable muscle spasms and stiffness without any neurological focus. Paradoxical reaction to midazolam and to propofol was diagnosed; difficult withdrawal was followed by favorable progression.

**Conclusion:** PR in the ICU context is exceptional. The present case is unique, with severe PR not only to midazolam but also to propofol. This etiology, with difficult withdrawal, should be considered after ruling out all classical etiologies for refractory agitation.

**Key words:** Hypnotics; Paradoxical reactions; Intensive care unit

## INTRODUCTION

Paradoxical reactions (PR) to benzodiazepines are well-known. PR can also follow sedation by propofol, although this has been reported only in the context of operating room anesthesia. We describe an original case of PR in intensive care unit (ICU) induced by midazolam and propofol.

## CASE SUMMARIES

A 78 year-old man with history of complete arrhythmia due to atrial fibrillation with blood-pressure elevation was admitted to the ICU for septic shock secondary to infectious pneumopathy. During the previous week, the patient had received 5 days' antibiotic therapy with amoxicillin for a respiratory infection. He was initially managed probabilistically with associated cefotaxime (intravenous injection, 2g/8h) and spiramycin (IV

injection, 1g/8h). Within 24 hours, the situation progressed to multiorgan failure and the patient was intubated and put on respiratory assistance for acute respiratory distress syndrome. Given the severity of presentation, antibiotic therapy was switched to piperacillin-tazobactam (IV infusion, 16 g/24h) and amikacin (IV injection 25 mg/kg/j for 3 days). Renal replacement therapy was initiated. No bacteria could be isolated.

Over the next 7 weeks hospital stay, there were 2 episodes of ventilator-acquired pneumonia, at days 7 and 22. Percutaneous tracheostomy was finally performed at day 40 due to the difficulty of ventilator weaning. The patient presented acute respiratory distress syndrome in a context of sepsis, without any bacterial isolates day 44.

Initial sedation used propofol and remifentanyl. At each propofol dose reduction after day 2, the patient immediately became restless and impossible to

communicate with; generalized muscle stiffness was accompanied by intense spasms. Midazolam was associated after 7 days and then used as the sole hypnotic. The slightest reduction in the dose of midazolam resulted in the same effects as with propofol. For 7 weeks, sedative dose reduction was attempted, withdrawing propofol, then midazolam and then both for several hours, tolerating the neurologic disorder. The patient remained systematically restless, with violent clonic episodes requiring restraint .

Clonidine (infusion rate of 1.5 µg/kg/h) and then effective-dose dexmedetomidine (infusion rate of 1 µg/kg/h) were introduced for possible withdrawal syndrome, without efficacy. Neuroleptics (haloperidol, oral dose up to 10 mg/days) also proved ineffective. Final diagnosis of PR was based on history and on ruling out other possibilities. Levetiracetam (oral dose 500mg/12h) was introduced for suspected convulsion, for which, however, repeated electroencephalogram found no evidence. Brain computed tomography and brain magnetic resonance imaging found no explanatory abnormalities. Lumbar puncture proved normal. Auditory evoked potentials showed no evidence of brainstem lesions; somatosensory evoked potentials found bilaterally conserved cortical response.

On day 49, low-dose muscle-relaxants (cisatracurium infusion rate of 0.1 mg/kg/h) was reintroduced to control clonic movements, with minimal sedation using remifentanyl (infusion rate of 0.2 µg/kg/min), dexmedetomidine (infusion rate of 1.4 µg/kg/h) and magnesium (bolus dose 3 g/4h) but no propofol or midazolam. Muscle-relaxants was again interrupted on day 51, and on day 52 visual contact was achieved for the first time. Involuntary movements progressively disappeared within 3 days. On day 53, the patient was responding to simple instructions and was calm. Mechanical ventilation via the tracheostomy was maintained only at night .

Over the next 10 days, intensive rehabilitation was implemented. Dialysis and artificial ventilation were finally withdrawn on day 60. The patient left the ICU on

day 70 for a geriatric department before transfer to after-care and rehabilitation.

## DISCUSSION

Under general anesthesia, sedation depth is unpredictable with most hypnotics (1), with wide inter-individual variation. Benzodiazepines have long been implicated in paradoxical excitement (2).

Propofol and benzodiazepines have similar action mechanisms, involving gamma-aminobutyric acid (GABA) receptor-chloride ionophore complex activation (3). Increased GABA activity leads to sedation, decreased anxiety, and possible reduction in perceived pain. Hypotheses are numerous, but the mechanism of this paradoxical response to benzodiazepines remains unclear (4). The mechanism is probably the same for propofol (5). In the present case, identical symptoms whether under midazolam or propofol could confirm that the mechanisms are similar .

There is no real definition of paradoxical excitement, and reactions are many and various. In Jeong et al.'s series, the most frequent were, like with benzodiazepines, relatively mild: disinhibited movement and loss of affective control (5). Severe forms comprise restlessness, jerking of the arms and legs, stiffening, no neurological focus, spontaneous movements and need to restrain the patient (5-7). The present patient presented such severe symptoms from the start, and contention was constantly needed whenever sedation was reduced, due to uncontrollable shaking; he showed no neurological focus. PR was thus diagnosed from severe symptoms on cessation of sedation, persisting several hours as the molecules presumably remained due to acute kidney failure and increased volume of distribution. The diagnosis was further confirmed by almost complete symptom resolution after two days without hypnotics .

Incidence of PR is unclear, varying greatly between reports. In the context of operating room sedation associated to local or regional anesthesia, incidence was

36% with propofol and 5% with midazolam (1). Anxiety is a risk factor for PR under propofol (8), as is advanced age (6). Alcohol acts via the same GABA receptor (9), and paradoxical excitement responses occur more frequently in alcohol drinkers (5).

In patients undergoing elective knee joint surgery under spinal anesthesia by propofol in target-controlled infusion, Jeong et al. (5) reported a higher rate of PR in the group receiving higher dose, suggesting a dose-effect. Thus, treating the PR by increasing the dose would not be a solution, unless to induce coma (5). In the present patients, dose had to be increased considerably to induce coma and prevent restlessness and intense shaking.

We chose finally to use non-GABA sedating medication including opioids for this episode. Opioids have proved effective against PR under sedation in gastroscopy (10). In a pediatric population with PR secondary to benzodiazepine premedication, ketamine proved effective (11). In this context, we also associated an  $\alpha$ 2-agonist to improve tolerance for the low-dose muscle-relaxants used to alleviate muscle stiffness and incontrollable clonic movement, awaiting total wash-out of propofol/midazolam.

Diagnosing paradoxical reaction in the intensive care setting can be difficult. Several factors were present that could have accounted for respiratory problems and restlessness during withdrawal: pulmonary condensation, uremia elevation, and possibly septic encephalopathy, confusion syndrome or withdrawal syndrome.

This observation tends to confirm similar action mechanisms for PR under propofol and benzodiazepine. It is a rare case of PR under midazolam and propofol in ICU, which should be considered in some cases of agitation when classical etiologies have been ruled out.

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