

# Fentanyl and Midazolam induced Respiratory Arrest and Neuromuscular Paralysis during Day Care Surgery

## A case report

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## توقف التنفس والشلل الكامل للعضلات بتأثير عقاري الفنتانيل والميدازولام أثناء إجراء الجراحة في الرعاية اليومية تقرير حالة

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**المخلص:** تم تسجيل حالة مريضة تبلغ من العمر 44 سنة تصنف على الدرجة الأولى حسب جمعية أطباء التخدير الأمريكية لإجراء عملية إستئصال ورم شحمي صغير من الفخذ الأيسر. حدث توقف عن التنفس مع شلل كامل للعضلات إستغرق قرابة 90 دقيقة ثم تسجيله عن طريق جهاز تحفيز الأعصاب بعد إعطاء المريضة جرعة ميدازولام (1 ملجم) وقينتانيل (100 مايكروجم) بالوريد لغرض تسكين الألم والتهدئة. بعد ذلك كانت الإفاقة طبيعية، ولم تكن هناك أية علاقة بين السبب والتأثير بين العقاقير والإستجابة غير الطبيعية لمفعولها.

**مفتاح الكلمات:** جراحة الرعاية اليومية، ميدازولام، فنتانيل، توقف التنفس، شلل العضلات، تقرير حالة، عمان.

**ABSTRACT:** We report a 44 year-old, American Society of Anesthesiologist Class I (ASA I), female patient scheduled for elective excision of a small lipoma of the left thigh. She went into a 90 minute apnea and complete muscle paralysis as evidenced by the absence of all stimulatory responses by a peripheral nerve stimulator after receiving midazolam (1.0 mg) and fentanyl (100 µg) intravenously for sedation and analgesia. The patient made an uneventful recovery after 90 minutes. No cause and effect relationship could be established between the administered drugs and this unusual response.

**Keywords:** Day case surgery; Midazolam, Fentanyl; Apnea; Muscle paralysis; Case report; Oman

**T**HE USE OF SMALL DOSES OF MIDAZOLAM and fentanyl is standard practice during day case surgery for providing sedation and analgesia during minor procedures under local anaesthetic infiltration. Although both midazolam and fentanyl are known to produce respiratory depression in the occasional patient,<sup>1</sup> complete apnea with total loss of train-of-four response on peripheral nerve stimulation has, as yet, been unreported. We here report a very unusual case of midazolam and fentanyl induced apnea with total skeletal muscle paralysis in a patient undergoing a small lipoma excision under local anaesthesia.

## Case Report

A 44 year-old, American Society of Anesthesiologist Class I (ASA I), female patient weighing 62 kg was scheduled for elective excision of a small lipoma of the left thigh in the supine position at Khoula Tertiary Hospital, Oman. The patient had undergone uneventful general anaesthesia on three previous occasions. Her last anaesthetic exposure was for lower segment caesarean section 9 years previously. We could not elicit any details about the nature of the anaesthetic used from her file or computer records. No abnormality was detected during the clinical examination and all her investigations were within acceptable limits. Her preoperative heart rate (HR) and blood pressure (BP) were 78/min and

126/64 mmHg respectively.

On the day of surgery, the patient received 7.5 mg of midazolam orally at 8:30am. The patient was taken to the operating theatre at 10:00am. After initiating non-invasive blood pressure, cardioscopic electrocardiography, peripheral oxygen saturation monitoring and intravenous (IV) infusion, the patient was administered 1.0 mg of midazolam and 50 + 50 µg of fentanyl IV. A Venturi mask (35% O<sub>2</sub>) was applied and the surgeon told to commence cleaning the surgical site. Over the next 3-4 minutes, the patient's respiratory pattern gradually changed, the oxygen saturation started falling and before the Venturi mask was removed, she had stopped breathing. Her respiration was immediately supported by positive pressure mask ventilation. Our immediate diagnosis was respiratory depression secondary to midazolam and/or fentanyl, especially keeping in mind the possible cumulative effect of 7.5 mg oral (premedication) and 1.0 mg intravenous midazolam. The patient's pupils were 2 mm and reactive to light. Two doses of naloxone (an opioid antagonist) 100 + 100 µg were administered 2-3 minutes apart. No positive response was noted. While flumazenil (a benzodiazepine antagonist) was being loaded and diluted for possible administration, a peripheral nerve stimulator (PNS) was applied for recording the level of neuromuscular blockade. Surprisingly, there was complete absence of response to train-of-four (TOF), double burst stimulation (DBS) and post tetanic count (PTC). At this juncture, the index of consciousness (IoC) monitor (IoC - ViewTm, Version 2.1, Morpheus Medical, Barcelona) was attached to the patient and the depth of sedation was noted to be 57. The IoC level transiently increased to 62 after the administration of 0.2 mg of flumazenil and subsequent doses of 0.1mg each to a total of 1.0 mg. During this brief period of 5-7 minutes, patient was noted to make shallow respiratory efforts. Surprisingly, the patient showed no response to TOF stimulation which was kept on a 12-second repeat mode. She went back to apnea thereafter. It was now decided to withhold all drug administration, pass a #4 laryngeal mask airway (LMA) and commence intermittent positive pressure ventilation with a tidal volume of 400 ml, respiratory rate of 12/min and a mixture of 2:1 each of air and oxygen. The patient continued to show absence of any response to peripheral nerve stimulation over the next 60 minutes. During this

period, her IoC level fluctuated between 54 and 67, BP and HR varied between 116/64-144/84 mmHg and 74-94/min respectively. This range of IoC suggested a borderline case between anaesthesia and a deep level of sedation (IoC level 99 = awake; 80 = sedation; 60-40 = general anaesthesia; 0 = isoelectric). Oxygen saturation remained between 98-100% and end tidal CO<sub>2</sub> 38-46 mmHg. Nearly 75 minutes after the administration of midazolam and fentanyl, the patient started making weak respiratory efforts and attempted to open her eyes. Over the next 30 minutes, she started breathing adequately (tidal volume 300-360 ml). Peripheral nerve stimulation now showed a weak response to TOF without a fade, but demonstrated a better response to DBS. Her IoC level was now 87. The LMA was soon removed on the patient's request and she was transferred to the recovery room for further observation. A fully restored TOF stimulation response was documented in the recovery room. Unfortunately, during the episode, no blood samples were collected to analyse drug levels to rule out any drug error. Viewed in retrospect, this should have been done.

With the approval of the attending anaesthesiologist, the surgeon removed the small lipoma after local infiltration with 5 ml of 0.25% bupivacaine. The surgery lasted 15 minutes. The patient made an uneventful recovery and was discharged from hospital the next day.

A detailed interview with the patient in the ward afterwards brought to light her tendency to feel weak and exhausted on returning from school where she was a teacher. Unfortunately, no evidence of myasthenia gravis or other skeletal muscle abnormalities could be detected as the patient refused further investigations.

## Discussion

Midazolam is frequently used in combination with opioids for anaesthesia and sedation.<sup>2</sup> Though respiratory arrest after low dose fentanyl alone has been rarely reported,<sup>3</sup> depression is most common when combined with a sedating agent such as midazolam or propofol.<sup>4,5</sup> Our patient had also received a combination of midazolam and fentanyl 3-4 minutes before she went into respiratory arrest. The duration of the respiratory depression was over one hour. This unexpectedly long duration of respiratory depression may be explained by

the fact that fentanyl is known to competitively inhibit metabolism of midazolam by cytochrome P450 3A4 (CYP3A4) activity<sup>2</sup> leading to prolonged apnea.<sup>1</sup> However the most interesting aspect of this case was the complete absence of neuromuscular junction activity as evident from total loss of TOE, DBS and PTC response by electrical stimulation with PNS. Inadvertent administration of muscle relaxants was ruled out as only the two drugs in question (midazolam and fentanyl) were prepared and administered before she went into apnea. As per operating theatre policy, all syringes of previous cases are always discarded. The fentanyl was undiluted, while 1 ml midazolam containing 5 mg was diluted to 1 mg/ml in distilled water. No other drug was administered which could have led to muscle paralysis and loss of PNS stimulation response. Moreover, had she received an accidental administration of muscle relaxant, a transient restoration of shallow respiration in response to flumazenil would not have been possible. However, in any future case, we would advocate collecting a blood sample to check blood levels for any drug error.

This leads us to an unexplored area of a possible interaction between the two drugs in question, especially midazolam, with any form of myopathy which the patient might have had. However, an exhaustive search of literature yielded no documentation or reference to interactions with midazolam and any form of myopathy leading to muscle paralysis. Midazolam by itself is known to possess a mild muscle-relaxant property, but it is mediated at the spinal cord level, not at the neuromuscular junction.<sup>6</sup> Interestingly, Fujii, Uemura and Toyooka<sup>7,8</sup> have reported midazolam induced diaphragmatic dysfunction in dogs in the form of reduced contractility and inhibited electrical activity, but how far this finding can be extrapolated

to human beings is uncertain.

## Conclusion

The present case highlights the possibility that monitored anaesthesia care under sedation (midazolam) and analgesia (fentanyl) for minor surgical procedure under local infiltration anaesthesia may produce profound central nervous system depression with resultant loss of consciousness, diaphragmatic dysfunction, and muscle tone necessitating respiratory support until full recovery.

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