

relationship between the night fall in PaO<sub>2</sub> and night fall in SaO<sub>2</sub> was such that, across a range of values of PaO<sub>2</sub>, the change in SaO<sub>2</sub> was generally greater for the group with nocturnal hypoxemia, which had lower day SaO<sub>2</sub> levels (Fig. 1b).

In conclusion, a sleep-related reduction in ventilation could be sufficient to explain the falls in night PaO<sub>2</sub> and SaO<sub>2</sub> seen in patients with cancer, with those with a lower day SaO<sub>2</sub> level more likely to experience a degree of nocturnal hypoxemia associated with impaired mental functioning. Further work, including more detailed sleep studies, is required to confirm our findings.

Andrew Wilcock, DM, FRCP  
Aqdas Kazi, MRCP  
Abi Walton, MRCP  
Matthew Maddocks, MCSP  
Department of Palliative Medicine  
Hayward House  
Nottingham University Hospitals  
NHS Trust  
Nottingham, United Kingdom

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### ***Acute Opioid Withdrawal Precipitated by Blood Transfusion in a 21-Year-Old Male***

To the Editor:

Cancer patients can be among the most challenging groups in which to maintain pain control. At our institution, many cancer patients are managed with patient-controlled analgesia (PCA) opioids, sometimes on an out-patient basis. These patients frequently undergo multiple surgeries as well as courses of chemotherapy and radiotherapy and, as

a result, often require multiple blood product transfusions. According to the American Association of Blood Banks standard,<sup>1</sup> blood transfusions should not be coadministered with any intravenous drugs or fluids apart from 0.9% sodium chloride. For many cancer patients, it is difficult or impractical to establish additional intravenous access solely for blood product administration, and therefore, the practice at our institution has been to disconnect any current intravenous infusion for the duration of blood product transfusion. Here, we describe a case of severe opioid withdrawal after disconnection of intravenous hydromorphone PCA and initiation of a blood transfusion.

### ***Case***

The patient was a 21-year-old, 46 kg, white male with a history of osteosarcoma of the right distal femur diagnosed 13 years earlier. He received chemotherapy and limb-sparing surgery. He developed a new focus of osteosarcoma in the left distal femur six years later, for which he underwent limb-sparing surgery and further chemotherapy. Two years later, a third focus of osteosarcoma was diagnosed in the left proximal tibia, for which he underwent left above-knee amputation. One year before the incident described in this case report, he presented with metastasis to the thoracic spine, for which he underwent surgery and radiation therapy.

The patient had experienced phantom pain after his amputation five years earlier, but it became especially troublesome after the spinal surgery. He required increasing doses of PCA hydromorphone for breakthrough pain while an inpatient and was discharged with PCA. At the time of the incident, his pain management regimen included oral modified-release oxycodone, 40 mg in the morning and 60 mg in the evening; hydromorphone intravenous PCA with a bolus of 3 mg every 10 minutes and no basal rate, gabapentin 900 mg three times daily, and amitriptyline 50 mg at bedtime. He considered his pain control to be adequate but continued to experience phantom pain episodes, especially when he became tired.

During the 13 years since diagnosis, the patient had received multiple transfusions of blood products, particularly during chemotherapy treatment. On the day of the incident,

he had been scheduled to receive transfusions of two units of platelets followed by two units of packed red blood cells (PRBCs) as an outpatient.

The patient's PCA was disconnected, and 50 mg of diphenhydramine was administered. The first unit (225 mL of platelets) was transfused over 43 minutes, the second unit (272 mL of platelets) over 45 minutes, and the third unit (207 mL of PRBCs) over 98 minutes.

During the transfusion of the PRBCs, the patient was sleeping but woke up and complained of feeling nauseated. When the unit was complete, he was noted to have facial flushing and profuse sweating. He complained of severe all over body pain, which he described as "someone stabbing him with needles" and of feeling like he was "on fire." His nausea intensified and he vomited twice. He had watery eyes and repeatedly stated that he did not "feel right." The patient also was noted to be yawning approximately once per minute.

Hospital personnel suspected a blood transfusion reaction and canceled the transfusion of the last unit of PRBCs. The empty transfused unit was returned to the blood transfusion service for testing. The patient received a further dose of intravenous diphenhydramine 50 mg and granisetron 1 mg. The patient's vital signs were temperature, 37.1°C; respiratory rate, 22 breaths per minute; blood pressure, 112/66 mm Hg; and heart rate, 116 per minute.

The patient's PCA was reconnected, and he self-administered a bolus of hydromorphone 3 mg. He immediately started to feel better and self-administered another two boluses of 3 mg 10 minutes apart. After the third bolus, the patient felt completely normal and was soon able to eat and drink. Severe acute opioid withdrawal during blood transfusion was diagnosed.

### **Comment**

Opioid withdrawal in this case was precipitated by blood transfusion. The patient was disconnected from his PCA for 186 minutes. After 137 minutes, he reported nausea, and by 186 minutes, when the unit of PRBCs was completed, he had developed an acute opioid withdrawal syndrome manifested by severe muscle

pains, sweating, nausea and vomiting, alternating episodes of hot and cold sensation, and frequent yawning.

The hospital personnel initially suspected a blood transfusion reaction, canceled the final unit, and treated the patient symptomatically. The patient's condition continued to deteriorate, and frequent yawning ultimately directed hospital personnel to the diagnosis of acute opioid withdrawal. The PCA was immediately reconnected, and after 9 mg hydromorphone, the patient returned to his normal condition.

Discontinuation of the intravenous PCA hydromorphone prior to blood product transfusion is a standard practice at St. Jude Children's Research Hospital, in compliance with the general advice from the American Association of Blood Bank Standards.<sup>1</sup> On reviewing the medical record, we found that the patient had never been disconnected from the PCA for more than 90 minutes and had never previously received more than two units of platelets or PRBCs at one time. On this occasion, he had received three units of blood products over 186 minutes. We surmise that the three hours without opioid administration, combined with the transfusion of blood products not containing opioids, which presumably caused dilution and further decline in plasma opioid concentration, precipitated withdrawal. At a weight of 46 kg and blood volume of approximately 3220 mL, the transfused blood product volume was calculated to represent 22% of his total blood volume.

Wozniak et al. showed that a low concentration of morphine infusion does not compromise PRBC transfusion.<sup>2</sup> In fact, the indicators of hemolysis, namely, potassium, plasma hemoglobin, and lactate dehydrogenase, only became significant at a morphine concentration of 10 mg/mL. Other studies have suggested that PCA may be safely coadministered with PRBCs.<sup>3,4</sup> The American Association of Blood Banks acknowledges this in the Technical Manual.<sup>1</sup> After an initial statement that no solutions other than 0.9% sodium chloride should be given with blood, it suggests that the coadministration of blood with hydromorphone and morphine may be undertaken with caution when no other intravenous access is available.

To our knowledge, this is the first case report of opioid withdrawal due to blood transfusion. We

believe that the patient developed withdrawal because of three factors. The first is that the patient had received long-term opioids and was opioid tolerant and physically dependent. The second is the relatively long discontinuation of the hydromorphone PCA, and the third factor is the transfusion of a relatively large volume of “opioid-free” blood. We suggest that extra care and attention should be given to the possibility of opioid withdrawal when a PCA is disconnected for blood product transfusion in a patient in whom opioid tolerance exists, and consideration should be given to the coadministration of morphine or hydromorphone in such cases.

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Roland N. Kaddoum, MD  
Laura L. Burgoyne, BM, BS  
Lilia A. Pereiras, MD  
George B. Bikhazi, MD  
Division of Anesthesiology  
St. Jude Children’s Research Hospital  
Memphis, Tennessee, USA

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