Opioid-induced neurotoxicity

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George, an 82-year-old man, had advanced chronic obstructive pulmonary disease (COPD) and was short of breath with minimal movement, as well as while eating and talking, despite maximum doses of bronchodilators via nebulizer and oral steroids. He'd had several hospitalizations for COPD exacerbation within a year and his forced expiratory volume in 1 second was 20% of expected. He used continuous oxygen via a concentrator. He also had serious congestive heart failure and his estimated glomerular filtration rate was 35 mL/min per 173 m^2 body surface area.

George had become quite frail and was no longer able to live on his own, so he had moved to a residential care facility. He had little or no cognitive impairment and was still able to enjoy visits from his daughter and grandchildren.

The physician started George on low-dose morphine (2.5 mg every 4 hours regularly) to help with dyspnea. The opioid worked well and the dose was gradually increased to 7.5 mg every 4 hours over the next 3 weeks. At that time the morphine was converted to a long-acting form of 20 mg every 12 hours with ongoing relief of his dyspnea. The constipation from the opioid was treated with daily lactulose.

A patient using opioids can develop opioid-induced neurotoxicity secondary to dehydration, infection, or drug interactions.

Two weeks later George developed increasing confusion, stopped eating, and vomited. His temperature was 38.1°C, pulse 92 beats per minute, blood pressure 140/90 mm Hg, and saturated oxygen 92% while receiving 3 L/min of oxygen. He was not coughing, but had complained of some dysuria in the day prior, so a urinary tract infection was presumed. He developed dehydration and drowsiness. The residential care facility sent George to emergency, where sepsis was diagnosed and treated. The opioid was presumed to be a major cause of confusion and drowsiness and was stopped. George was less drowsy but remained agitated and confused for several days. The confusion was managed with loxapine and did clear somewhat, so he returned to the facility on the fourth day with oral antibiotics.

Upon George's readmission to the facility, his nurses noted the prominent shortness of breath. He was still confused. The physician was called and asked to prescribe for the shortness of breath, but due to discontinuation of the opioid in acute care, the physician chose to increase the oxygen to 4 L/min and ordered loxapine for confusion. George continued to be very short of breath and was anxious and agitated. The physician then ordered 0.5 mg of lorazepam every 8 hours, which caused prolonged somnolence and confusion but at least did reduce the dyspnea and anxiety. The staff believed that the dyspnea should be treated even if it meant George would be sedated and confused. After several days of not eating or drinking, he was clearly declining. A decision was made not to return him to acute care, as he had overwhelming illness. He died several days later.

What could have been done differently?

While George's death was inevitable because of his advanced disease, could the journey have been any different? Were opioids the cause of his confusion?

George had advanced cardiopulmonary disease that was causing dyspnea. His physician correctly started opioids for dyspnea. A meta-analysis of opioids for dyspnea has shown benefit in advanced disease of any cause.[1] Opioids are safe in advanced cardiopulmonary disease providing one starts with a low dose and increases it slowly.

George developed delirium 2 weeks after reaching the therapeutic dose of opioids. Up to that time he had been stable with no signs of opioid toxicity. When he developed sepsis, he became dehydrated, which precipitated opioid toxicity—referred to as opioid-induced neurotoxicity (OIN).

Multifactorial syndrome

Opioid-induced neurotoxicity is a multifactorial syndrome that causes a spectrum of symptoms, from mild confusion or drowsiness to hallucinations, delirium, and seizures.[2] It can occur with any opioid but is more likely to occur when using opioids with active metabolites, such as meperidine, codeine, morphine, and (to a lesser degree) hydromorphone. Oxycodone has active metabolites, but whether they are clinically significant is debatable.[3] There are no active metabolites of fentanyl or

methadone. In frail older adults who have any signs of OIN, it is best to rotate to another opioid, preferably one with no active metabolites. Patients who have severe renal failure[4] or who are frail should start with an opioid that has few or no active metabolites. Opioid-induced neurotoxicity typically develops within a few days to a week of initiating an opioid or reaching a dose of opioid that causes metabolite buildup. Factors such as dehydration, infection, or adding drugs that depress the central nervous system can tip a frail older adult into opioid toxicity.

What were George's tradeoffs?

George's delirium resulted from the urinary infection on top of OIN secondary to infection and dehydration. The tendency in delirium is to stop all drugs that could cause the confusion. When an opioid has been given for pain or dyspnea, the better solution would be to reduce the dose or switch to an opioid that is less likely to cause OIN. In George's case the opioid could have been switched to hydromorphone or oxycodone at a reduced dose. With rehydration and treating the infection, the OIN would have cleared and George's dyspnea would have remained under optimal control.

The physician was reluctant to use an opioid for dyspnea again and instead treated the dyspnea with a medication that can cause prolonged somnolence or paradoxical reaction in older adults. There is little evidence to support benzodiazepine treatment of dyspnea except that it reduces the associated anxiety.[5] If an adjuvant to opioids for dyspnea is needed, a small, regular dose of methotrimeprazine will be more effective.

The staff and the physician did achieve their intention, which was to treat George's dyspnea and actively manage his symptoms to the end of his life. Choosing opioids best suited for frail older adults[6] or those with renal failure, and knowing how to manage OIN without stopping opioids necessary for symptom control, however, would have improved the quality of George's last days and might have extended his life.

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BOTTOM LINE

- Opioids are indicated for dyspnea with advanced disease of any cause.
- Opioid-induced neurotoxicity can be common in frail older adults and those with renal failure. Opioids with few or no active metabolites are generally better tolerated.
- A patient who has been receiving a stable dose of an opioid for more than 2 weeks is unlikely to develop OIN unless dehydration, infection, or a drug interaction has precipitated it.
- Opioid-induced neurotoxicity is managed by rotating the opioid and by rehydration. Opioids should not be discontinued if they are needed for pain or dyspnea.

POINTS SAILLANTS

- Les opiacés sont indiqués pour la dyspnée à un stade avancé d'une maladie, quelle qu'en soit la cause.
- La neurotoxicité provoquée par les opiacés peut être fréquente chez les adules frêles plus âgés et ceux atteints d'insuffisance rénale. Les opiacés ne contenant aucun métabolite actif ou en contenant peu sont généralement mieux tolérés.
- Un patient qui reçoit une dose stable d'opiacés depuis plus de 2 semaines ne développera probablement pas de neurotoxicité provoquée par les opiacés, sauf si elle est déclenchée par une déshydratation, une infection ou une interaction médicamenteuse.
- On traite la neurotoxicité provoquée par les opiacés en faisant une rotation entre les opiacés et en réhydratant. On ne devrait pas cesser les opiacés s'ils sont nécessaires pour la douleur ou la dyspnée.

References

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