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REPORT

Nebulized Fentanyl for Dyspnea in a Hospice Patient with True Allergy to Morphine and Hydromorphone

Robert G. Wahler, Jr. , David B. Smith, and Kimberly B. Mulcahy

ABSTRACT

An 86-year-old white female was admitted to hospice care with lung cancer. Even with optimal medical management, she suffered from dyspnea and required opioid therapy. However, the patient had a true morphine and hydromorphone allergy. She was administered nebulized fentanyl for symptomatic relief of dyspnea with good effect and she did not experience any allergic response.

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Introduction

Opioids often rightly evoke caution and anxiety in health providers who prescribe, recommend, and dispense them. Respecting the serious nature of the tolerance, dependence, addiction, and respiratory depression associated with opioids is necessary. However, in cases where an additional layer of concern such as a reported “allergy” is confronted, knowledge of opioid pharmacology and toxicology is required to provide patients with suitable opioids to meet their particular need.

True opioid allergies are rare. Instead, typical side effects, such as stomach upset, are commonly misinterpreted and documented as an allergy.¹ A true allergy is a reaction that is mediated by allergen-specific immunoglobulin E (IgE), requires prior exposure to the offending agent, and can result in hives, maculopapular rash, erythema multiforme pustular rash, bronchospasm, and angioedema.¹ Conversely, a pseudoallergy typically does not require a prior exposure to the offending agent, can be related to potency, dose, or route of administration, and is mediated by histamine release from mast cells and basophils causing itching, flushing, sweating, hives, tachycardia, and hypotension.¹ Allergic responses should not be confused with adverse effects such as nausea, vomiting,

or constipation that are commonly but erroneously referred to as allergies in a patient’s medical history.¹ A thorough patient history should always be obtained in order to not attribute an adverse reaction of a co-ingested medication, food, or environmental factor to opioid administration. For example, a postsurgical patient with delirium should not be labeled as “opioid allergic,” as the delirium is likely a multifaceted response to opioids, other medications including anesthesia, surgical trauma, and the environment of the recovery process.¹

An allergy to a medication can contraindicate the use of a specific drug and potentially an entire drug class in a patient. In order to avoid a subsequent reaction, in the case of opioids, pharmacologic substitutions that have a different molecular structure or pharmacokinetic and pharmacodynamic properties can be made.

Opioids are categorized into three structural subclasses: phenanthrenes (codeine, hydrocodone, oxycodone, morphine, hydromorphone, levorphanol, and pentazocine), phenylpiperidines (fentanyl and meperidine), and diphenylheptanes (methadone and propoxyphene).¹ Patients with an allergy to one structural subclass of opioids may be treated by an opioid from another structural subclass and are less likely to experience an allergic reaction to the new agent.¹

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Table 1. Summary of allergic reactions.

Classification	Mediators	Clinical features
Type I: anaphylaxis	IgE	Urticaria, angioedema, pruritus, cardiorespiratory (anaphylactic) shock, asthma, rhinitis, or conjunctivitis
Type II: semidelayed	IgM or IgG, antibody-mediated cytotoxic reactions	Fever and infection due to agranulocytosis, purpura due to thrombocytopenia, or immunoallergic hemolytic anemia
Type III	IgM immune complex-mediated reactions	Serum sickness (fever, general ill feeling, hives, itching, joint pain, rash, swollen lymph nodes); serum sickness-like disease (fever, urticarial polycyclic wheals with central clearing, oral edema without mucosal involvement, lymphadenopathy, arthralgias, myalgias, and mild proteinuria)
Type IV	Lymphocytes delayed-type hypersensitivity	Skin eruptions (contact dermatitis), potentially maculopapular rash, erythema multiforme
Pseudoallergy histamine	Direct histamine release from mast cells	Pruritus, urticaria, red man syndrome.
Pseudoallergy complement	Nonimmunologic complement activation, histamine release	Pruritus, urticaria
Pseudoallergy	Aberrations in arachidonic acid products	Intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin

Note. Adapted from Descotes et al.¹⁶

There are limited data about cross-sensitivity among the drug classes due to the rare occurrence of true opioid allergies, and any opioid use in a patient with a reported allergy should be done with caution.¹ The risks and benefits of utilizing opioids should be weighed, and a patient's previously recorded reaction can help determine the appropriateness of therapy. For instance, if a patient experienced hives and itching, which can be either allergy or pseudoallergy, an alternative opioid may be prescribed at a lower dose with a concurrent antihistamine. However, if a patient had an anaphylactic reaction, the risk of drug use may result in requiring the use of a different subclass or new class of medications entirely.¹ Specifically, morphine causes a greater histamine release than hydromorphone and fentanyl, which could influence the decision of the choice of medication if choosing a new opiate agent.

Dyspnea occurs in 10%–70% of patients with end-stage cancer and 90%–95% of patients with chronic obstructive pulmonary disease (COPD). The frequency and severity of episodes of dyspnea and symptom distress can negatively impact the quality of life of the patient in hospice and their caregivers.^{2–4} Although treating the underlying cause of dyspnea is preferred, this is not always plausible in end-stage disease for which symptom management is paramount.⁵ Parenteral and oral opioids have been widely studied and are drugs of choice for management of dyspnea in the palliative setting.^{2–5} Opioids have a rapid onset of action with relief noted to occur within 15 to 30 minutes.⁴ Opioids administered using a nebulizer or intranasally have an even faster onset of action and reportedly provide analgesia within 5 minutes, lasting up to 1 hour.^{3,4,6–10} The rapid alleviation of patient distress is extremely beneficial for episodes

of dyspnea, which typically last for only 20 minutes or less.^{3,4} Inhaled opioids are believed to bind to and modulate intrapulmonary opioid receptors in the tracheobronchial tree and alveoli, which in turn relieve dyspnea.⁸ Although inhaled, there is systemic absorption of fentanyl ranging from 12% to 100%, which also can account for some dyspnea relief by modulating central opioid receptors in the brainstem, medulla, and pons.^{11–13} Due to systemic absorption, patients may experience typical opioid side effects, such as drowsiness and sedation, and also route-specific adverse effects, such as airway irritation from the inhaled opioid or excipients.^{9,13} In recent literature, fentanyl has shown to be potentially advantageous over morphine via nebulizer due to the former drug's high potency, short duration of action, and high lipid solubility.^{2–4,6,8–10}

This patient had a true allergy to both morphine and hydromorphone with a documented reaction of hives and rash. We describe the course of events when facing the dilemma of providing opioids for the relief of dyspnea.

Case description

An 86-year-old white female was admitted to our hospice home care program with a terminal diagnosis of squamous cell carcinoma of the right lung established via biopsy. She had undergone repeated chemotherapy and radiation treatments and reportedly had a poor response. Prior to hospice admission she had multiple emergency room (ER) visits for dyspnea. Concomitant disease states included systolic heart failure (ejection fraction: 35%–40%) and COPD (forced vital capacity [FVC]: 42%, forced expiratory volume

Table 2. List of medications prior to inpatient unit admission.

Medication	Administration
Budesonide/formoterol	160 μ g/4.5 μ g inhaler (Symbicort); 2 puff(s) inhale twice a day
Ipratropium/albuterol	0.5–3 mg/3 mL solution, 1 UD via nebulizer every 4 hours as needed
Montelukast	10 mg tablet by mouth daily
Alprazolam	0.5–1 mg by mouth four times a day
Bumetanide	0.5 mg by mouth twice a day
Metoclopramide	10 mg by mouth three times a day as needed
Diphenhydramine	1–2 tablets by mouth every 4 hours as needed
Senna-S	1–2 tablets by mouth every day as needed
Magnesium oxide	400 mg by mouth twice a day
Multivitamin	1 tablet by mouth every day
acidophilus with bifidus	Chew 1 tablet by mouth every day
fish oil	1 capsule by mouth every day
Ciclopirox 0.77% cream	Apply topically to the affected areas daily
Hydrocortisone 1% cream	Apply topically to affected areas every day

Note. UD = unit dose.

in 1 second [FEV₁]; 32%). Past history included anxiety, depression, hyperlipidemia, hypertension, atrial fibrillation, and coronary artery disease. The patient's respiratory medications included montelukast sodium 10 mg by mouth at bedtime, budesonide/formoterol 160 μ g/4.5 μ g two inhalations twice a day, and albuterol sulfate/ipratropium bromide one nebule (3 mL) via nebulizer every 4 hours as needed as well as oxygen and bilevel positive air pressure (BiPap). The complete medication list is given in Table 2.

Due to frequent episodes of dyspnea while in hospice home care, an opioid was considered to augment her existing dyspnea treatment. Upon admission to hospice home care, no allergies to opioids had been documented. Morphine was provided utilizing the 100 mg/5 mL concentrated liquid at a dose of 5 mg sublingually every 2 hours as needed for dyspnea. Four days later, an urgent nursing visit found the patient presenting with hives. The patient then admitted that she had pruritus since starting morphine but that it had helped her dyspnea. Upon further query, the patient's son recalled that the patient had a severe hives reaction to hydromorphone during a previous hospitalization. These allergies were then documented in the electronic health record; however, further investigation, which may have differentiated true allergy from pseudoallergy, was not conducted.

Faced with this dilemma, the hospice clinical pharmacist was approached for further consultation. Instead of using morphine or hydromorphone, a review of several references^{1,3} resulted in determining that fentanyl would be an alternative due to it being subcategorized as a phenylpiperidine opioid and not

Table 3. Medication list—inpatient.

Medication	Administration
Fentanyl injection	50 μ g via nebulizer every 3 hours as needed for dyspnea
Ipratropium/albuterol	0.5–3 mg/3 mL solution, 1 UD via nebulizer four times daily
Dexamethasone	2 mg tablet by mouth daily
Lorazepam	0.5 mg IV every 4 hours as needed for anxiety
Montelukast	10 mg tablet by mouth daily
Bumetanide	0.5 mg by mouth twice a day
Metoclopramide	10 mg by mouth three times a day as needed
Diphenhydramine injection	50 mg IM every 4 hours as needed
Epinephrine	0.5 mg IM as needed, may repeat every 10 minutes $\times$ 1
Senna-S	1–2 tablets by mouth every day as needed
bisacodyl suppository	1 suppository (10 mg) per rectum daily as needed for constipation
magnesium oxide	400 mg by mouth twice a day
multivitamin	1 tablet by mouth every day
acidophilus with bifidus	Chew 1 tablet by mouth every day
fish oil	1 capsule by mouth every day
Ciclopirox 0.77% cream	Apply topically to the affected areas daily
Hydrocortisone 1% cream	Apply topically to affected areas every day
Al/Mg hydroxide suppository	30 mL by mouth every 4 hours as needed
Bisacodyl suppository	10 mg suppository rectally every day; rectally

Note. UD = unit dose.

a phenanthrene opioid like morphine and hydromorphone. To be cautious, the patient was transferred from home care to our inpatient unit for acute management of her symptoms of dyspnea and closer observation in consideration of her opioid allergies. Preservative-free injectable fentanyl solution 50 μ g/mL and normal saline were utilized to prepare a 25 μ g/2 mL solution to be inhaled via nebulizer every 3 hours as needed. Epinephrine and diphenhydramine were ordered as needed for anaphylaxis, pruritis, or hives. Her respiratory therapy medications were maintained, and other therapy modifications can be noted in the new medication list in Table 3.

On day 1, the patient received fentanyl 25 μ g/2 mL and the albuterol/ipratropium nebules once, both with positive effect. There was no report of itching or hives in response to the fentanyl. Albuterol/ipratropium was switched to around-the-clock dosing on the second day and fentanyl was increased to 50 μ g every 3 hours to increase the duration of dyspnea relief. The patient continued to use fentanyl 50 μ g three to four times a day with albuterol/ipratropium nebules with continued positive effect.

Budesonide/formoterol was discontinued on day 6 of her inpatient stay for perceived lack of benefit in

the patient's condition and oral dexamethasone 2 mg daily was begun. Her fentanyl use also reduced to twice daily on her seventh day of inpatient treatment and further decreased to once a day on days 9, 11, and 12, but the patient and family still reported positive effect from medication use when administered.

As the care plan was to discharge the patient to her home, fentanyl 25 µg/hour patch every 72 hours was added to provide around the clock dyspnea relief. Methadone 2.5 mg every 3 hours as needed for pain was also prescribed for the patient, with consistent use two to five times per day until her passing. There were no further complaints of dyspnea despite the albuterol/ipratropium dosing being changed from every 4 hours around-the-clock to every 4 hours as needed. The patient's family reported continued dyspnea relief on this regimen until the patient's passing on day 18 of therapy.

Discussion

Sublingual concentrated morphine solution is commonly considered the therapy of choice for symptom relief of dyspnea in hospice and palliative care patients, consistent with current evidence-based medicine.¹⁴ Because there was a reaction to both the high-histamine-release morphine and the low-histamine-release hydromorphone, we felt this was a case of true opioid allergy. Due to the patient's allergy to morphine and hydromorphone, we utilized a high-potency opioid of a different structural class in order to reduce the risk of a reaction. Since there are limited data on cross-sensitivity among opioid classes, epinephrine and diphenhydramine were also ordered in case of an allergic response, but in this case they were never used.

Fentanyl injection was selected for use in this case for a variety of reasons. The pharmacokinetics of fentanyl includes a short duration of action, which was an additional safety parameter in case the patient developed an allergy despite precautions.¹⁰ The solution is preservative free, therefore eliminating any additional irritants that could cause histamine release and bronchospasm.^{3,4} Fentanyl injectable solution was readily available, whereas other formulations of fentanyl delivery (e.g., lozenges, buccal tablets and film) would require special order, delay the patient's treatment, and add significant cost. Newer fentanyl products were not available at the time of this case.

Although controversy exists with the use of the nebulized route for administration of opioids for

dyspnea,¹⁵ we chose this route as an alternative to home administration of parenteral fentanyl based upon pragmatism. An assessment of the patient's home and caregiving situation determined that managing injections was a significant barrier whereas the use of nebulized medications was readily acceptable to the caregivers.

Objective data were lacking, since dyspnea relief is predominately a subjective event. The patient would report feeling "better" after nebulized fentanyl administration, and she would be found comfortably resting. The patient was switched to transdermal fentanyl, which allowed for a constant administration of drug and may have provided sustained effects on dyspnea. Since there were no further complaints of dyspnea, we may be able to assume transdermal fentanyl is effective in dyspnea relief as well. The patient's subjective reports could also have been due to additional pain relief, as many of the reports on inhaled fentanyl measured analgesic response.

Other opioids are commonly used by nebulized delivery for management of dyspnea symptoms, and other nebulized medications are being explored.⁴ Inhaled morphine has been used for relief of dyspnea in advanced illness; however, it has the potential for side effects in patients due to systemic absorption through the respiratory tract. Fentanyl may be a suitable alternative in patients with a morphine allergy; however, it has a high lipophilicity and will also be extensively absorbed through the respiratory tract and can also cause systemic adverse effects.^{2-6,10,11} This patient did not experience any complications, and both inhaled and transdermal fentanyl appeared to provide beneficial effects in alleviating her dyspnea.^{4,5}

Randomized controlled trials are difficult to conduct in a palliative care setting, which complicates finding evidence for novel drug use.^{2,4,5} Most publications supporting the use of nebulized opioids for relief of dyspnea are case reports and systematic reviews, and these have not detected a benefit of nebulized opioids.^{14,15} Well-designed and adequately powered studies are needed to confirm the effectiveness and safety in patients with a reported allergy to an opioid in a different structural class.³

Conclusions

This case reports successful treatment of a patient with a true allergy to morphine and hydromorphone who safely utilized nebulized fentanyl for management of her dyspnea. Fentanyl administered via the nebulized

route should be considered as treatment for dyspnea when contraindications to phenanthrene opioids exist.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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