PALLIATIVE PEARLS
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Conversion from Transdermal Fentanyl Use to Oral Administration in Cachectic Patients September 2020

PATIENT CASE

DS is a 76-year-old male admitted to hospice 3 months ago with a primary diagnosis of lung cancer with metastases to the bone. Comorbidities include hypertension and COPD. He lives at home with his wife.

Current medications:

- Transdermal fentanyl (TDF) 75 mcg; Apply 1 patch topically every 72 hours for pain
- Morphine 15mg tablet; Take 1 tablet by mouth every 4 hours as needed for pain
- Senna 8.6 mg; Take 2 tablets by mouth twice a day for constipation
- Dexamethasone 4 mg; Take 2 tablets by mouth every morning for pain and breathing
- Ipratropium-albuterol; Inhale 1 vial via nebulizer 4 times a day and every 4 hours as needed for shortness of breath
- Albuterol HFA inhaler; Take 2 puffs by mouth every 4 hours as needed for shortness of breath
- Lisinopril 10 mg; Take 1 tablet by mouth every morning for high blood pressure

Pain for DS was managed on Fentanyl 50 mcg every 72 hours for approximately 2 months however he recently began experiencing achy and dull pain in his chest area and legs and began taking his breakthrough morphine more frequently. The morphine is keeping his pain well managed. To reduce his pill burden and provide a longer duration of pain control, his fentanyl patch was increased to the 75-mcg strength. After 3 days he reports no improvement in the duration of pain control and has continued to take breakthrough morphine around the clock. He has had significant weight loss over the last 3 months (approximately 8% of his body weight) and has been diagnosed with cachexia. Although he doesn't have much of an appetite, he is not having any difficulty with swallowing. The prescriber is considering increasing the fentanyl patch strength again and has asked for your input.

CACHEXIA OVERVIEW

Cachexia, or involuntary weight loss, is a syndrome of progressive and ongoing loss of skeletal muscle mass (with or without loss of fat mass) and may be the result of an underlying disease such as cancer, AIDS or COPD. Cachexia cannot be fully reversed by conventional nutritional support and is associated with an increase in mortality.[1] It is theorized that cachexia is the result of the increase of inflammatory mediators present in these chronic illnesses that work in conjunction with hormonal mediators to cause catabolism, proteolysis, increase in energy expenditure and decreased appetite. Patients may present with additional symptoms such as nausea, unfavorable changes in taste and smell, repulsion to meat, early satiety or glucose intolerance. Consensus defines cachexia as one of the following:[1,2]

- Weight loss greater than 5% within the past 6 months (in the absence of starvation)
- BMI less than 20 and weight loss greater than 2%

- Sarcopenia and weight loss greater than 2%

TRANSDERMAL FENTANYL (TDF)[3,4]

Transdermal fentanyl (Duragesic®) is released at a constant rate into the skin creating a depot of medication in the upper epidermis. It is then absorbed systemically from this depot. Fentanyl is highly lipophilic and is 80 to 85% bound to protein. Serum concentrations reach peak approximately 20 to 72 hours after the first application. Steady state is achieved by the end of the second 72-hour patch application. It is recommended to increase TDF doses no more frequently than every 3 to 6 days. The patch should be applied to a flat, intact, non-irritated and non-irradiated area of the body such as the chest, flank, back, or upper arm. Due to the potential for temperature dependent increases in release of fentanyl from the transdermal system, avoid application site and surrounding skin exposure to heat sources (e.g., heating pads, hot tubs, saunas).

CACHEXIA AND TDF

TDF is indicated for the management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for whom alternative treatment options are inadequate. TDF is useful for those with swallowing difficulties or who struggle adhering to traditional dosing regimens (i.e., multiple doses per day).

When converting current opioid therapy to TDF, oral morphine equivalents must be calculated first. Once obtained, utilize a 2.4:1 ratio to convert from oral morphine equivalents to an equivalent TDF strength (oral morphine 2.4 mg/day = TDF 1 mcg/hr). For example, 60 mg of oral morphine per day is equivalent to a 25 mcg/hr TDF patch.

Oral Morphine to Fentanyl Patch Equianalgesic Conversion:[5,6]

Oral morphine 2.4 mg/day = TDF 1 mcg/hr

- 60 mg = 25 mcg
- 120 mg = 50 mcg
- 180mg = 75 mcg
- 240 mg = 100 mcg
- 300 mg = 125 mcg
- 360 mg = 150 mcg
- 420 mg = 175 mcg
- 480 mg = 200 mcg

The practice of adjusting the “oral morphine equivalent to TDF” conversion ratio to account for theorized lower TDF absorption in cachectic patients is largely unsupported in the literature. Considering how TDF is absorbed, in theory, it makes sense that less subcutaneous fat on a patient would result in less TDF absorbed. However, clinically, effects vary and are entirely patient-specific. However, it is still important to recognize the roots of this practice (see below) and to

manage opioid conversions and patient pain accordingly. If a cachectic patient has not responded to a recent dose increase of TDF, TDF may not be the best route of administration. At this point, perform a pain assessment to ensure an opioid is still appropriate, use the last effective TDF patch strength to perform any future opioid conversion calculations, and be liberal with breakthrough dose administration.[6]

- Heiskanen T, et al[6,7] compared 10 cancer patients with cachexia to 10 patients without cachexia found that fentanyl plasma concentrations were significantly lower at 48 and 72 hours after patch administration in patients with cachexia. However, no additional evidence has been published to support these findings.
- A 2013 study by Nomura and colleagues,[6,8] evaluated the relationship between serum albumin and the absorption of fentanyl as a secondary study outcome in 19 patients that were converted from intravenous fentanyl to TDF. The results showed fentanyl concentrations were significantly lower in those who had low serum albumin. Fentanyl is highly protein bound, mostly to albumin. Patients with cachexia may have low albumin due to "transcapillary leak into subcutaneous and muscle interstitial spaces". Davis M,[6,9] in an editorial of Nomura and colleagues' study, discussed that transcapillary leakage into subcutaneous and interstitial spaces can be up to 300% higher in patients with cachexia. Fentanyl may bind to the interstitial albumin, which may reduce fentanyl blood levels.

PATIENT CASE ASSESSMENT & RECOMMENDATIONS

DS has experienced significant weight loss, has not responded to an increase in TDF strength, however has responded to oral morphine around-the-clock. This may indicate that he is not achieving therapeutic levels of fentanyl via the transdermal route.

A recommendation is made to convert TDF to oral morphine extended-release. To reduce the risk of potentially converting to a dose that may be too high for him to tolerate, use the last effective dose of TDF, or 50 mcg/hr (=120 mg oral morphine/day) for DS.[6] Calculate the morphine breakthrough dose as 10-20% of the total daily dose, or 12 to 24 mg for DS, and encourage its use.

Conversion Goals:

- Discontinue TDF
- Initiate morphine extended-release (ER) 60 mg tablet, 1 tablet by mouth every 12 hours for pain
- Increase breakthrough regimen dose to morphine 15mg tablets, 2 tablets (30 mg) by mouth every 3 hours as needed for pain

Transition Steps:[8]

- Remove TDF patch
- For the first 12 hours after patch removal, use only the rescue opioid for pain (morphine 15 mg tablet, 2 tablets (30 mg) by mouth every 3 hours as needed for pain)

- Twelve hours after patch removal, begin with 50% of the calculated scheduled opioid regimen, (morphine ER 30 mg by mouth every 12 hours) and continue to offer rescue opioid as needed
- Twenty-four hours after patch removal, increase to 100% of the calculated scheduled opioid regimen, (Morphine ER 60 mg by mouth every 12 hours) and continue to offer the rescue opioid as needed

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