Clinical Resource Guide: Transdermal Fentanyl

INTRODUCTION TO TRANSDERMAL FENTANYL

Fentanyl is a synthetic opioid with pharmacologic activity similar to that of morphine, oxycodone, hydromorphone or hydrocodone. However, several distinct differences should also be noted. First, fentanyl is a phenylpiperidine derivative, meaning its chemical structure differs from that of the previously mentioned opioids. Therefore, it can be used as a viable alternative for a patient with a morphine (or other phenanthrene) allergy. Secondly, fentanyl is about 75 to 100 times more potent than morphine (on a mg-to-mg basis), making understanding of equianalgesic conversion principles essential when considering initiation or transitioning to fentanyl. Third, fentanyl is highly lipophilic (lipid soluble), making the transdermal patch formulation a possibility due to the ability of the drug to pass into subcutaneous tissue where a depot is formed before being absorbed into the plasma. The lipophilic properties of fentanyl also result in the rapid diffusion across the blood-brain barrier, resulting in a quick onset of action once absorbed from the administration site. Finally, due to the uptrend in illicit fentanyl use, some patients and/or loved ones may have developed preconceived notions related to using fentanyl as an analgesic, which should be discussed prior to prescribing.

Pharmacist Corner Objectives

1. Describe the pharmacokinetics of transdermal fentanyl
2. Understand variables that may impact dosing of transdermal fentanyl
3. Recommend an appropriate dose of transdermal fentanyl when switching from another opioid
4. Describe the appropriate timing of fentanyl transdermal patch placement in relation to last dose of opioid transitioned from
5. Outline a strategy for switching from transdermal fentanyl to another opioid regimen

ROLE OF TRANSDERMAL FENTANYL IN THE HOSPICE SETTING

In the Palliative Care and Hospice setting, transdermal fentanyl is used primarily as an analgesic, with pain relieving benefit documented in the treatment of neoplasm-related pain, and could be considered for refractory, non-malignant chronic pain for opioid tolerant patients. The transdermal delivery system allows the medication to be considered for use if patients are

unable to safely take medications by mouth. Similar to methadone, fentanyl can be used for patients with impaired or worsening kidney function, but in the case of fentanyl, this is due to the lack of active metabolites. However, fentanyl lacks the additional mechanisms of action that make methadone particularly effective for the management of neuropathic pain (NMDA receptor antagonism, serotonin-norepinephrine reuptake inhibition).

Candidates for Therapy

- True phenanthrene class (morphine, oxycodone, hydromorphone) allergy
- Significant renal impairment
- Patients unable to swallow tablets, but with persisting pain

Patients Who Should Not be Considered for Therapy

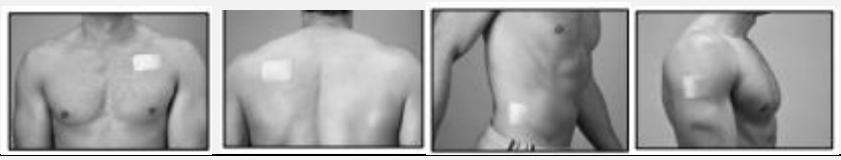
- Patient with very limited prognosis (hours to days to live)
- Significant drug interactions and no viable alternatives for interacting medications
- Patients with widespread skin rash or condition leaving limited space for patch application
- Limited support, concern for compliance with medication regimen

Transdermal Fentanyl Patch Doses and Approximate Cost

Dose	Cost/Patch	Cost/30 days	30-day Morphine Equivalent Cost
12mcg/hr	$10.00	$100.00	$17.00
25mcg/hr	$4.00	$40.00	$24.00
37.5mcg/hr	$40.00-$50.00	$400.00-$500.00	$41.00
50mcg/hr	$5.00-$10.00	$50.00-$100.00	$54.00
75mcg/hr	$7.00-$10.00	$70.00-$100.00	$78.00
100mcg/hr	$10.00	$100.00	$104.00

Transdermal Fentanyl Patch Administration

When determining where to apply the transdermal fentanyl patch, consider the following manufacturer recommendations:

Transdermal Fentanyl Patch Recommendations for Administration
1.) Patches can be safely applied to the chest, back, flank or upper arm in a place where there is no hair. 
2.) For children or patients with behavioral issues or terminal delirium, recommend patch placement on the upper back to lower chances of being removed by the patient

3.) **DO NOT** place a fentanyl transdermal patch on skin that is burned, cut, irritated or damaged
4.) Avoid sensitive areas or those with frequent motion
5.) If there is hair at the preferred site of application, **DO NOT** shave, as shaving may irritate the skin. Instead, clip hair as close to the skin as possible, using scissors. 

PHARMACOKINETICS OF TRANSDERMAL FENTANYL

Transdermal fentanyl is absorbed through the skin, producing a drug depot in the upper skin layers, which then diffuses into systemic circulation.

Time After Placement	Pharmacologic Response
0-12 hours	• Subcutaneous depot forming, little anticipated analgesic activity • PRN opioid usage may increase during this time if transitioning from another long-acting opioid to transdermal fentanyl
12-24 hours	• Diffusion from formed depot into systemic circulation begins • Initial analgesia from fentanyl experienced, not full response
24-36 hours	• Full effect of analgesia from transdermal fentanyl experienced
36-72 hours	• Steady state achieved; patch due to be changed after 72 hours

Transdermal Fentanyl Considerations

Use in cachectic patients

- Variability of patient response to transdermal fentanyl has been reported in patients with low body weight or cancer-related cachexia
- Lower plasma fentanyl concentrations at 48 hours and 72 hours in cachectic patients (mean BMI 16kg/m^2) as compared to normal body weight (mean BMI 23kg/m^2) has been reported.
- Proposed explanation for lower serum concentration of fentanyl in patients with low body weight is related to lower serum albumin in this population, as fentanyl is 70% protein bound
- Albumin can be lower in patients with cachexia due and reduced in patients with cancer or inflammatory disorders due to transcapillary leak, which can be increased by up to 300% in patients with cancer cachexia

Impact of increased temperature on transdermal fentanyl absorption

- Elevated body temperature (104°F) can increase fentanyl absorption by approximately 1/3.
- Fever, heating pads, electric blanket, hot baths, tanning beds, saunas, hot tubs, or heated water beds may result in increased fentanyl absorption
- Patient/caregiver counseling regarding avoiding these scenarios while using fentanyl is important

Fentanyl serum concentration following stopping therapy

- After removal, serum fentanyl levels fall by approximately 50% in the following 20-27 hours
- This slower rate of serum concentration decline is attributed to fentanyl continuing to be absorbed into the serum from the depot after the removal of the patch until the depot is depleted.
- Understanding this, when transitioning from transdermal fentanyl, it is appropriate to wait 24 hours before starting the full replacement dose of a different long-acting opioid after removing the patch

TRANSDERMAL FENTANYL DOSING EQUIVALENCIES

Although multiple conversion ratios have been noted in literature over years, steady-state trials of opioid conversions provide some clarity to this question. Steady state trials provide more robust data than single-dose crossover trials. Results from these studies indicate the following conversion factors should be used:

Transdermal Fentanyl Dose Conversion Ratios	
Converting from fentanyl to another opioid	Fentanyl 25mcg/hr = morphine 60mg/day
Converting from another opioid to fentanyl	Morphine 100mg/day = Fentanyl 40mcg/hr*

*These calculations may need to be rounded to the nearest patch strength

SUMMARY

Transdermal fentanyl is a potent opioid analgesic with the potential to provide alleviation of pain in patients with a severe, life-limiting illness. Its transdermal formulation allows for sustained analgesia in patients unable to take oral opioid therapy, but assessment and counseling must be provided to ensure safe and appropriate administration. Due to a lack of active metabolites, fentanyl does not require renal dose adjustment, and can in patients with renal impairment or worsening renal function. Despite appropriateness of use for many hospice patients with pain, and improved clarity in dosing guidance, the use of transdermal fentanyl is more expensive than an equivalent regimen of long-acting morphine or methadone. Fentanyl is also not as effective for the management of neuropathic pain as methadone, and the transdermal patch formulation is not as versatile as methadone. For questions regarding patient-specific scenarios, please call Better RX for a Pharmacy Consultation.

References:

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