CHAPTER 5

Transdermal and Parenteral Fentanyl Dosage Calculations and Conversions

OBJECTIVES

After reading this chapter and completing all practice problems, the participant will be able to:

1. Describe the pharmacokinetics of transdermal fentanyl, and variables that can influence dosing.
2. Recommend an appropriate dose of transdermal fentanyl when switching from other opioids, including rescue opioid dosing. The participant will be able to describe the appropriate timing of this conversion.
3. Recommend a strategy for switching from transdermal fentanyl to another opioid regimen, including dosing and appropriate timing.
4. Describe how to transition between intravenous (IV) fentanyl and transdermal fentanyl.

INTRODUCTION

Fentanyl is a synthetic pure mu opioid agonist with pharmacologic properties similar to morphine, hydromorphone, oxycodone and other opioids. Important differences about fentanyl include its high degree of potency (about 75–100 times more potent than morphine on a mg-to-mg basis), and greater lipid solubility than morphine. The lipophilic nature of fentanyl facilitates rapid diffusion across the blood-brain barrier, resulting in a quick onset of action once the drug is absorbed from the administration site. Fentanyl is available in several dosage formulations, and may be administered by the following routes for a variety of pain-related indications:

- *Parenteral*—fentanyl may be given by intravenous (IV) injection, IV infusion, subcutaneous (SQ) infusion or intramuscular (IM) injection (although we already agreed that an IM analgesic is an oxymoron, and this practice is discouraged). It is used parenterally preoperatively, intraoperatively and postoperatively, and is occasionally used for the management of severe acute and chronic pain in other clinical situations. Preservative free fentanyl has been injected or infused epidurally or intrathecally by specialist practitioners.
- *Transdermal*—we have had transdermal fentanyl patches (TDF; also referred to as "fentanyl transdermal system") available for many years; this formulation relies on passive diffu-

sion (drug moving from an area of higher concentration [the transdermal patch] to an area of lower concentration [the skin]); this formulation is indicated for the management of cancer and non-cancer pain for patients whose pain cannot be controlled with less intensive analgesic therapy (e.g., non-opioids, or intermittent dosing with short-acting opioids), and who are opioid-tolerant.

- *Buccal* and *transmucosal* fentanyl, as discussed in the previous chapter, are immediate release dosage forms approved to treat breakthrough pain in cancer patients.
- Other rapid-acting fentanyl products are in various stages of development. A *"fentanyl iontophoretic transdermal system"* has been developed for the short-term management of acute post-operative pain in adults, although it is not clear if this product will make it to market. The drug is delivered on patient demand, with an electrical charge driving the drug into the skin. Another transdermal fentanyl electrical enhancement delivery system under development uses *electroporation* technology. With this delivery system high voltage electric pulses of extremely short duration enhance skin permeability and consequently, fentanyl absorption.

In this chapter we will focus on conversion calculations involving switching to and from transdermal fentanyl, and conversion calculations involving IV fentanyl.

Transdermal Fentanyl

Transdermal fentanyl patches were designed to provide long-lasting opioid therapy (three days) for patients with stable chronic pain. Because fentanyl has a low molecular weight and high solubility in both fat and water, the drug is a good candidate for transdermal administration. There are 5 patch strengths currently available: 12 mcg/h (actually it delivers 12.5 mcg/h, but is referred to as 12 mcg/h to avoid a medication error by mistaking the intended dose to be 125 mcg/h), 25 mcg/h, 50 mcg/h, 75 mcg/h and 100 mcg/h. The dose is determined by the surface area of the patch, therefore the patches are larger as the dose increases.[1]

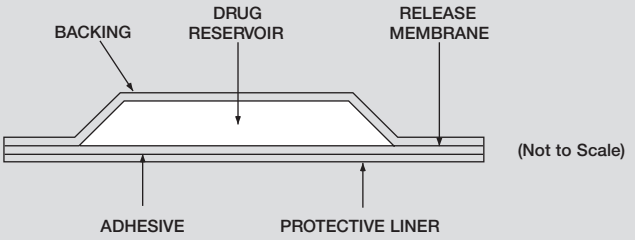
Pharmacokinetics

Transdermal fentanyl is formulated as both a gel-containing reservoir and a drug-in-adhesive matrix patch (see Sidebar: Transdermal Fentanyl Patch Formulations). Manufacturer's guidelines state that the TDF patch should be applied to an intact, non-irritated and non-irradiated flat skin surface such as the chest, back, flank or upper arm. If necessary, hair should be clipped (not shaved) at the site of application. Fentanyl is absorbed through the skin, producing a drug depot in the upper skin layers, then diffusing into the systemic circulation. On average minimally effective blood concentrations of fentanyl are seen in about 12 hours, and the time to maximum concentration is approximately 36 hours.[1] It may take up to 3 to 6 days to ultimately reach steady-state serum concentrations with TDF.

It is important to recognize that transdermal drug delivery is fraught with variability from patient to patient. Even when considering any given patient, there are variables that can affect fentanyl absorption. For example, an elevated body temperature (e.g., 40°C [104°F]) increases fentanyl absorption by about one third.[1,2] So when you hear that a patient has been tucked into bed, "snug as a bug in a rug" you might want to think about increased body temperature. This also applies to use of electric blankets, heating pads, tanning beds, sunbathing, hot baths, hot tubs, saunas and heated

TRANSDERMAL FENTANYL PATCH FORMULATIONS

The first TDF product on the market was the branded product, Duragesic. This formulation is a gel-containing reservoir and shown in the diagram:



This formulation results in significant interindividual variability with 60–84% of the fentanyl absorbed in most patients. Conversely, 28–84.4% of the original fentanyl content remains in the patch after 3 days use. Subsequent to this initial formulation of TDF, newer formulations use a drug-in-adhesive matrix layer. These two formulations have been shown to be bioequivalent.[5,6]

water beds.[3] In one recent case example, a patient on TDF for residual hip pain after a nasty construction accident (who insisted he had to apply his patch directly over the site of the pain) accidentally discovered the "bonus dose" effect of applying a heating pad directly over the patch. Obviously this practice should be strictly discouraged. There have been several fatalities reported due to nonadherence to this warning.

Another variable that is frequently talked about is the use of TDF in cachectic, low body weight patients. The Duragesic® package insert states "Duragesic® should be used with caution in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics due to poor fat stores, muscle wasting or altered clearance."[4] Many practitioners claim that cachectic patients do not respond as well as expected to TDF, and may report little or no improvement in pain when increasing the patch strength. Unfortunately there is no evidence base currently to support this claim. Despite the lack of evidence, opioid conversion calculations skills while mostly science, still have an artful component. If a cachectic patient has not responded to recent dosage increases in TDF, it may be wise to use the *last* effective patch strength upon which to base conversion calculations and be liberal with rescue opioid dosing (more on this later).

Another important pharmacokinetic parameter to consider when doing opioid conversion calculations involving TDF is how slowly the fentanyl serum concentration falls after patch removal. After removal, serum levels fall gradually; about half the drug has been eliminated after 17 hours.[4] Obviously it takes longer for the fentanyl serum concentration to fall after patch removal as compared to ending an IV infusion of fentanyl, since fentanyl continues to be absorbed from the depot in the upper layers

of the skin continuing to diffuse into the systemic circulation even after the patch is removed. Knowledge of this pharmacokinetic parameter is of particular importance when converting a patient *from* TDF to another opioid. For example, it would be prudent to wait 24 hours or longer before starting the full replacement dose of a different long-acting opioid after removing the TDF patch. Rather, the practitioner would encourage use of the rescue opioid during that time period.

Other Important Considerations

We have seen that there are many misconceptions about the appropriate use of TDF among health care providers, occasionally resulting in avoidable morbidity and mortality. One recent survey questioned physician knowledge of TDF dosing strategies including initial dosing, use of rescue opioids with the patch, converting to and from TDF, and how to manage escalating pain in a patient receiving TDF.[7] Physicians who routinely prescribed TDF were more knowledgeable than less frequent prescribers about the appropriate use of TDF, but overall knowledge and confidence in using TDF was poor. The bad news is that failure to completely understand these dosing principles may result in patient harm, including death. The good news is that they will probably want to buy this book!

The Food and Drug Administration has released two public health advisories in recent years with safety warnings about TDF due to increased serious side effects and deaths from fentanyl overdose. Some precautions listed in the Healthcare Professional Advisory released in December 2007 are as follows[8]:

"Recommendations and Considerations for Healthcare Professionals:

- The fentanyl patch is indicated for the management of persistent, moderate to severe chronic pain in opioid-tolerant patients 2 years of age or older who require a total daily opioid dose at least equivalent to fentanyl transdermal system 25 mcg/h. Opioid-tolerant patients are those who have been taking daily, for a week or longer, at least 60 mg of oral morphine, 30 mg of oral oxycodone, or at least 8 mg of oral hydromorphone or an equianalgesic dose of another opioid. Fentanyl patch use in non-opioid tolerant patients has resulted in fatal respiratory depression.
- Consult the prescribing information to determine the initial fentanyl patch dose. Overestimating the dose when converting patients from another opioid analgesic can result in fatal overdose with the first dose.
- The fentanyl patch is contraindicated in the management of post-operative pain, mild pain, or intermittent pain (e.g., use on an as needed basis) because of the risk for serious or life-threatening respiratory depression. Fatalities from fentanyl overdose have occurred in these situations.
- Concomitant use of the fentanyl patch with any cytochrome P450 3A4 inhibitors (such as ketoconazole, erythromycin, nefazodone, diltiazem, or grapefruit juice) may result in an increase in fentanyl plasma concentrations, which may cause potentially fatal respiratory depression. Carefully monitor patients concomitantly taking cytochrome P450 3A4 inhibitors and using the patch for an extended period of time and adjust the fentanyl dose if necessary."[8]

As shown above, the FDA recommends starting a TDF patch of 25 mcg/h or greater only in patients who are opioid tolerant. The Duragesic® package insert states that TDF is contraindicated[4]:

- "In patients who are not opioid-tolerant [NOTE: Prescribing information does *not* exclude the 12 mcg/h TDF patch from this contraindication)
- In the management of acute pain or in patients who require opioid analgesia for a short period of time
- In the management of post-operative pain, including use after out-patient or day surgeries (e.g., tonsillectomies)
- In the management of mild pain
- In the management of intermittent pain (e.g., use on an as needed basis [prn])"

Probably the two big "take-home" messages from these warnings are that TDF is inappropriate for acute pain management, for intermittent or mild pain management, and should not be used in opioid-naïve patients. Therefore, our discussion of "starting doses" of TDF will focus on conversion calculations from other opioid regimens.

Regarding the 12 mcg/h TDF patch, the package labeling states that there have been no systematic evaluation of Duragesic as an initial opioid analgesic in managing chronic pain, including the 12 mcg/h patch. The package labeling states once again that TDF should only be used in patients who are opioid-tolerant.

PITFALL

Transdermal Fentanyl—Too Much of a Good Thing?

The Duragesic® prescribing information warns about death and serious medical problems that have occurred when people were accidentally exposed to TDF.[4] Examples of accidental exposure include transfer of a TDF patch from an adult's body to a child while hugging, accidentally sitting on a patch and possible accidental exposure of a caregiver's skin to fentanyl in the patch while applying or removing a patient's patch. One reported case of caregiver toxicity involved the mother of a 40 year old patient receiving 600 mcg/h of TDF every 36 hours.[9] Due to skin irritation, the caregiver sprayed the patient's skin with the corticosteroid fluticasone propionate prior to patch application and applied beclomethasone cream, another corticosteroid, to the application site when the patch was removed. The author hypothesized that the effects of opioid intoxication experienced by the caregiver were likely exacerbated by the use of corticosteroids which may have enhanced transdermal fentanyl absorption, the caregiver's application technique, and the high dosage involved.

It is also important to counsel patients, families and caregivers on the appropriate disposal of used and unused TDF patches. The manufacturer of Duragesic brand transdermal fentanyl recommends that unused patches should be folded in half so the adhesive side adheres to itself, and immediately flushed down the toilet after removal from the skin. Unused patches should be similarly disposed of. Simply folding the patch in half and discarding in the trash does not preclude a child or pet retrieving and playing with the patch, potentially leading to fatality. Practitioners should be aware of, and adhere to any local or state guidelines regarding disposal of discontinued medications such as TDF, especially if they differ from the recommendations described here.

Converting TO Trandermal Fentanyl—Equivalent Dosing

When converting to TDF, it is important that the patient's pain be under relatively stable control prior to the conversion. It is too difficult to chase increasing pain with a drug delivery system (such as a transdermal patch) that can take up to 6 days

to achieve steady state serum levels. Initial dose-finding with TDF takes longer to achieve pain relief and carries a greater risk of adverse effects as compared to using a short-acting oral opioid.

Given a patient with stable pain control that we want to convert to TDF, what is the process we use? As you will see in the next few paragraphs, there are many approaches that are used. We will start by examining what is reported in the manufacturer's insert and then review selected literature which support the conversion ratio most practitioners use today. Hang in there with me and you'll be a pro in no time at all!

Let's look at the conversion process suggested in the Duragesic package insert[4]:

- Determine the patient's 24-hour opioid requirement (don't forget to add in rescue medication consistently use for non-volitional incident and spontaneous pain)
- If the patient was not already receiving oral morphine, convert their 24-hour opioid to oral morphine equivalents using a conversion chart and process as explained in previous chapters and shown in Chapter 1, Table 1-1. (Note: do *not* reduce the morphine equivalent amount to account for lack of complete cross-tolerance).
- Consult a conversion table that provides an equianalgesic recommendation from oral morphine to TDF. The conversion chart provided by the manufacturer's of Duragesic is shown in Table 5-1.[4]
- Initiate treatment with the recommended dose, and titrate dosage upward no more frequently than every 3 days after administering the initial dose or every 6 days thereafter until analgesic efficacy is reached.

Sounds so straightforward, doesn't it? Well, you wouldn't be reading this chapter if it was *that* easy!

Table 5-1

Conversion from Oral Morphine to Duragesic[4]

Recommended Initial Duragesic® Dose Based on Daily Oral Morphine Dose

Oral 24-hour morphine (mg/day)	Duragesic® dose (mcg/h)
60–134	25
135–224	50
225–314	75
315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1034	275
1035–1124	300

In the package insert for Duragesic® the manufacturers are clear that the starting TDF dose determined from using the table above is likely too low for 50% of patients. This manufacturer-provided conversion guideline has been criticized for having morphine ranges that are too broad, and for being based on opioid conversions that have also been criticized.[10] For example, the guidelines shown above convert oral to parenteral morphine at a 6:1 ratio (which is based on single-dose studies) instead of the more accepted 3:1 ratio associated with chronic administration. Other cited inaccuracies include an oral morphine to oral hydromorphone ratio of 8:1, and an assumption that methadone is 3 times the potency of morphine and equipotent when given parenterally.[10] The consequences of underestimating the correct TDF strength are more than just merely an inconvenience necessitating increased use of the rescue medication. There have been at least four published case reports of patients experiencing a withdrawal syndrome when converting from oral opioids to TDF.[11] You would not be *wrong* to use this conversion guideline to switch to TDF, just recognize that it is extremely likely the TDF dose will be too low to meet patient needs. On the other hand, if a patient is taking a cytochromic P450 3A4 inhibiting medication (e.g., ketoconazole, erythromycin, nefazodone, diltiazem or grapefruit juice) use of this conversion chart may result in a TDF starting dose that will require less titration to achieve pain relief because the interacting drug will reduce fentanyl metabolism, resulting in an increased fentanyl serum level. Last, the manufacturer's guidelines are very clear that the table shown above, which is admittedly conservative, should *not* be used to convert *from* TDF to oral morphine.[4] If the table is purposefully conservative going *to* TDF, it would be too *aggressive* converting *from* TDF.

We know that fentanyl is 75–100 times more potent than morphine.[12] Keep your eye on the ball as we think this through:

- 100 mg oral morphine per day ~ 1 mg (1000 mcg) fentanyl per day (transdermal or IV)
- Therefore, 60 mg oral morphine per day ~ 0.6 mg (600 mcg) fentanyl per day
- 0.6 mg (600 mcg) fentanyl per **day** (24 hours) = 25 mcg per **hour** (25 mcg/h) fentanyl (transdermal or IV)—we just divided the TDD by 24 to determine the hourly dose of fentanyl

Therefore, **60 mg oral morphine per day** is about equivalent to **25 mcg/h of TDF**
Donner and colleagues evaluated this ratio in 98 cancer patients who were on sustained-release oral morphine and whose pain was stable, using the morphine:TDF equivalencies shown in Table 5-2.[12]

Table 5-2

Donner Recommended Conversion from Oral Morphine to Duragesic

Recommended Initial Fentanyl Doses Based on Daily Oral Morphine Dosage[12]

24-Hour oral morphine dose (mg/day)	Transdermal fentanyl dose (mcg/h)
30–90	25
91–150	50
151–210	75
211–270	100
Every additional 60 mg per day	An additional 25 mcg per hour

Patients were converted to transdermal fentanyl patches, which were changed every 72 hours and titrated to pain relief. Oral morphine solution was used for breakthrough pain. Their results showed that pain control was equivalent between sustained release morphine and TDF, but that patients on TDF used more oral morphine solution for breakthrough pain. Slightly more than 40% of patients achieved sufficient pain relief with the initial TDF dose. The remainder required a dosage increase. The authors concluded that using the 100:1 (oral morphine:transdermal fentanyl) ratio is safe and effective, but that the actual ratio is probably closer to 70:1.

Are you still with me—here comes the best part! Building on the model that 60 mg oral morphine is approximately equivalent to 25 mcg/h of TDF, and having research that shows even this is a bit conservative (although no where near as conservative as the manufacturer's recommendations), it was a small leap to the conversion that most practitioners (including this author) use today, which is:

- Use a 2:1 ratio $\longrightarrow$ every 2 mg oral morphine per ***day*** ~ 1 mcg per ***hour*** TDF
- Another way to word this is the number of mcg per ***hour*** of TDF should be about half the number of milligrams of oral morphine per ***day***
- For example, 50 mg per day of oral morphine ~ 25 mcg/h TDF

Breitbart and colleagues popularized this recommendation, offering the following process to convert to TDF[13]:

- Determine the total daily dose of oral morphine required to control patient's pain (or the equivalent based on their current opioid regimen; refer to Table 1-1).
- Use a conversion of 2:1 (mg oral morphine per day to mcg/h of TDF) to calculate the mcg/h dose of fentanyl.
- Once an approximate mcg/h dose for fentanyl is calculated, round up or down based on the available patch strengths (12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h or 100 mcg/h) and based on the patient's pain level and overall clinical status. If the patient's pain is well controlled, round down to the next patch strength. If the current opioid regimen is not adequately controlling the pain, consider rounding up to the next patch strength.

The American Academy of Hospice and Palliative Medicine Fast Fact on "Converting To/From Transdermal Fentanyl"[14] also cites Breitbart and colleagues. They further recommend that the 2:1 (mg oral morphine per day to mcg/h of TDF) may be excessive in opioid-naïve patients and/or the elderly. (Note: we're not supposed to be starting TDF in opioid-naïve patients! Thought you had me, didn't you!). When in doubt, they recommend rounding down to the closest patch strength, and being liberal with rescue medication. While we have not described how these folks calculated an appropriate rescue opioid dose, we will do so during our case exercises. You didn't think I'd leave you hanging, did you?

Well I can't speak for you, but I'm exhausted after thinking all that through! Let's look at a case!

CASE 5.1

Switching from Oral Long-acting Morphine to TDF

JR is a 72 year old woman with esophageal cancer. Her pain has been well controlled on MS Contin 60 mg by mouth every 12 hours, with morphine oral solution 20 mg every 2 hours as needed for breakthrough pain. She has been using about two doses per day of the morphine oral solution, and this regimen has kept her comfortable. Unfortunately she is having increased difficulty swallowing the MS Contin tablets. How would we convert her to TDF? Let's take a closer look—step by step, inch by inch…

Step 1—Assess the patient's pain: We have assessed JR's pain, and it's well-controlled. We are only switching her to TDF because of swallowing difficulties.

Step 2—Determine the patient's total daily dose of their current opioid: JR is taking MS Contin 60 mg po q12h (120 mg oral morphine) plus two doses of morphine oral solution 20 mg (an additional 40 mg) for a grand total of 160 mg oral morphine per day.

Step 3—Decide which opioid to switch to, and consult conversion chart: we already know we're switching to TDF. Using our guidelines of 2:1 oral morphine mg per day : TDF mcg per hour, we calculate a dose for TDF of 80 mcg/h.

Step 4—Individualize the dosage and ensure adequate access to breakthrough pain medication: Because TDF is not available as 80 mcg/h, we must either round down to 75 mcg/h or round up to 100 mcg/h. JR is elderly, and her pain is well controlled, therefore it seems prudent to round down to the 75 mcg/h strength. Let's discuss the issue of breakthrough pain in a moment.

Step 5—Patient follow-up and reassessment: We will discuss the timing of switching to and from TDF below, but we must always remember to monitor our patient carefully during and after the transition. But we're not done with JR! This case raises several additional issues. First, how do we time the transition from MS Contin to TDF? Also, what do we do for breakthrough pain?

Because it takes 12–16 hours to achieve therapeutic fentanyl serum levels, we must provide the patient with opioid coverage during the conversion period. In cases such as JR, she should take one last dose of MS Contin (60 mg) at the same time the TDF is applied. This last dose of sustained release morphine (which lasts 8–12 hours) will be tapering off as the TDF is kicking in. JR should also continue to have the same dose of short-acting morphine available for breakthrough pain, as this dose has been effective for her.

If JR is too weak to swallow one last sustained-release morphine tablet prior to application of the TDF, she should receive at least two to three doses of short acting morphine after the TDF is applied. In other words, instead of taking one last MS Contin 60 mg tablet, if she can't swallow it, instead she would be given MSIR 20 mg at time zero (time of patch application), 4 hours after patch application, and 8 hours after patch application. These three 20-mg doses equal the 60-mg dose she would have received from that one last MS Contin tablet.

This same principle should be followed for any patient who was receiving only short-acting opioids around-the-clock prior to TDF conversion. Let's look at a patient taking MSIR

10 mg q4h around the clock, with MSIR 5 mg every 2 hours for additional pain, being switched to TDF 25 mcg/h. When the 25 mcg/h TDF patch is applied, the patient should continue to receive their regularly scheduled MSIR 10 mg every 4 hours for at least two or three more doses. Keep the "prn" MSIR 5 mg q2h order in place for additional pain relief.

This brings us to the question of *which* opioid to use for breakthrough pain when patients are using TDF for persistent pain. We discussed this at length in the previous chapter—our options are buccal or transmucosal fentanyl, or short-acting/immediate-onset morphine, oxycodone, hydromorphone, or oxymorphone. There is no compelling reason why we *must* use the same opioid for the persistent pain and the breakthrough pain, and the rapid-acting fentanyl products are fairly expensive compared to the more traditional opioids. However, if you decide the use of a rapid-acting fentanyl product is appropriate, following the dosing guidelines as discussed in the previous chapter. Remember, there is *no* reliable correlation between the TDF patch strength and the appropriate starting dose of rapid-acting fentanyl. You must begin with the lowest available rapid acting fentanyl dose and titrate per recommended guidelines.

If the patient had been using a short-acting opioid for breakthrough pain successfully prior to conversion to TDF, they can continue taking the same opioid at the same dose once they convert to TDF. This is permissible because the patient's pain is stable and we are not increasing or decreasing the total daily dose of oral morphine (or equivalent dose of another opioid) other than to accommodate patch strength availability. However, if the patient did not have a short-acting opioid available we can still calculate a ballpark starting dose for breakthrough pain. For example, if a patient had been receiving Kadian 100 mg po per day prior to conversion to TDF, a reasonable dose of short-acting morphine would have been 10–15 mg (using our 10–15% of the TDD rule to determine the dose for breakthrough pain). If the patient was switched to TDF 50 mcg/h, it would be appropriate to also recommend MSIR 15 mg po q2h prn breakthrough pain. Of course you would follow the same guidelines as discussed in the previous chapter to determine if this were an appropriate dose or not. Let's look at another case, shall we?

CASE 5.2

Switching from Multiple Opioids to TDF

KG is a 52 year old woman with a history of pancreatic cancer, admitted to your hospital with a complaint of significant nausea with oral ingestion of food or medications, and occasional vomiting. Her analgesic regimen is as follows:

- TDF 25 mcg/h
- OxyContin 20 mg po q12h
- Hydromorphone 4 mg po q2h prn breakthrough pain, using on average 6 doses per day

You would like to roll all of this into TDF due to the nausea. What's the first step? As I'm sure you recall, the first step is to do a careful assessment of the pain and determine if an opioid is the best treatment of KG's pain. Perhaps she needs a co-analgesic added. Let's assume we've done the assessment and feel that switching entirely to TDF is the best plan. Step 2 is to perform an accurate accounting of how she has been taking her opioids. Importantly, with a complaint of nausea and occasional vomiting, it is important to

determine how much of her opioid regimen she has received over the past 24–48 hours (e.g., to be alert for possible opioid withdrawal, etc.). Let's assume she has experienced only very occasional vomiting, and it doesn't significantly affect her total daily opioid use.

Step 2 is to convert her OxyContin and hydromorphone to an equivalent dose of oral morphine. Her total daily dose of oxycodone is 40 mg—how much oral morphine is this approximately equivalent to? Using Method A (e.g., simple ratio) we know that the oral oxycodone:oral morphine ratio is 20:30 (see Table 1-1: Equianalgesic Opioid Dosing Table). Using this we calculate that 40 mg oral oxycodone is equivalent to 60 mg oral morphine. You can also use Method B:

Actual Drug Doses: **Equianalgesic Data from Chart:**

$$\frac{\text{“X” mg TDD new opioid}}{\text{mg TDD current opioid}} = \frac{\text{equianalgesic factor of new opioid}}{\text{equianalgesic factor of current opioid}}$$

Let's fill in the numbers:

$$\frac{\text{“X” mg TDD new opioid}}{\text{40 mg oral oxycodone}} = \frac{\text{30 mg oral morphine}}{\text{20 mg oral oxycodone}}$$

We cross multiply:

(30) × (40) = (X) × (20)

1200 = 20X

X = 60

This method also shows that 40 mg oral oxycodone per day is approximately equivalent to 60 mg oral morphine per day.

Now we need to do the same exercise with the oral hydromorphone the patient has been using for breakthrough pain. She is taking on average six doses of hydromorphone 4 mg, which gives us a total daily dose of 24 mg oral hydromorphone. How much oral morphine is this approximately equivalent to?

$$\frac{\text{“X” mg TDD new opioid}}{\text{24 mg oral hydromorphone}} = \frac{\text{30 mg oral morphine}}{\text{7.5 mg oral hydromorphone}}$$

Cross multiply:

(30) × (24) = (X) × (7.5)

720 = 7.5X

X = 96

We see that 24 mg oral hydromorphone per day is approximately equivalent to 96 mg oral morphine per day.

If we add the oral morphine equivalent we got from the oxycodone calculation (60 mg) to the oral morphine equivalent from the hydromorphone calculation (96 mg) we have determined the patient is receiving an equivalent dose of 156 mg of oral morphine per day.

PEARL

A Critically Important Point to Note at This Juncture Is as Follows

When switching from one opioid to another, we discussed how we usually reduce the dose of the new opioid by 25–50% to allow for incomplete cross-tolerance. **We do not do this** *when doing the calculation for the purposes of converting to TDF. The incomplete cross tolerance factor has already been taken into account when making the jump from oral morphine (or oral morphine equivalent) to TDF. You will see this same concept discussed in the next chapter on methadone dosing. The converse holds true as well; when we convert* **from** *TDF to oral morphine, the "lack of cross tolerance" factor has already been considered.*

OK, back at the ranch—the patient is receiving approximately the equivalent of 156 mg oral morphine per day. Half of this is 78—which would represent 78 mcg/h TDF. Obviously we don't have a 78 mcg/h TDF patch, so we would round down to 75 mcg/h (this is Step 4—individualization for the patient). Also, don't forget the goal of this exercise was to combine all the opioids the patient was receiving into one opioid—TDF. She's already on TDF 25 mcg/h. If we add 75 mcg/h based on the calculations we've just done, we could discontinue the OxyContin and hydromorphone, and increase the TDF from 25 mcg/h to 100 mcg/h.

The next burning question is, "How do we time all this?" If she is able to swallow it, the patient should receive her last OxyContin 20 mg tablet at the same time the TDF patch is changed from 25 mcg/h to 100 mcg/h (or a 75 mcg/h patch added), if she is able to swallow it. If she is too nauseated to take anything by mouth, discontinue both the OxyContin and hydromorphone, and switch to TDF 100 mcg/h. You will then need to rely on a non-oral route of administration to provide a rescue opioid. Your options are parenteral or rectal. How do we calculate the dose for both routes assuming we want to use morphine? This is hurting your head to use skills you learned in previous chapters isn't it? I know you can do it—keep the faith!

OK, let's recap. We have calculated that TDF 100 mcg/h will probably maintain the level of comfort she had initially on her three-opioid regimen (OxyContin, TDF 25 mcg/h and hydromorphone for breakthrough pain). TDF 100 mcg/h is approximately equivalent to 200 mg per day of oral morphine. Ten to fifteen percent of this is 20–30 mg, therefore we could offer morphine rectal suppositories 20 mg q2h prn breakthrough pain, and increase to 30 mg rectal morphine as needed. Alternately, if you want to provide a SQ injection of morphine as needed, we need to convert the 200 mg TDD oral morphine to parenteral morphine. As you recall, 10 mg parenteral morphine is equivalent to 30 mg oral morphine, therefore her TDD of parenteral morphine would be about 66 mg. Ten to fifteen percent of 66 mg is 6.6–10 mg, therefore an appropriate dose of SQ morphine would be 7.5 or 10 mg q2h prn breakthrough pain.

One last note about the timing of this conversion. Let's say the patient had her current 25 mcg/h TDF patch placed 24 hours ago. You have two options when converting to TDF 100 mcg/h. You could add a 75 mcg patch now, and at the end of 48 additional hours you could remove *both* the 25 and 75 mcg/h patches (which is technically a day earlier than when we would have to change the 75 mcg/h patch) and replace with a 100 mcg/h

TDF patch. Or, you could remove the 25 mcg/h TDF patch when you admitted the patient and switch immediately to a 100 mcg/h TDF. As stated earlier, it will take a minimum of 12 hours to see a clinically meaningful increase in fentanyl serum concentrations with the new patch addition, and at least 36 hours (if not 3–6 days) to achieved maximum steady-state concentrations.[1] The last step is to carefully monitor the patient during and after this transition to assure an optimal therapeutic outcome.

PITFALL

"Set and Forget" Method Akin to "You Snooze, Your Patient May Lose"

Many providers feel that once a TDF patch is "set" in place on the patient, you can walk away and "forget" about the patient for 3 days. Wrong-O! You MUST continue to use good clinical judgment and monitor your patient regularly. If the patient is becoming overmedicated on fentanyl, you will need to take special precautions to reverse the opioid intoxication for hours and hours after patch removal. Similarly, TDF is not a cure-all; patients still need to be monitoring for responsiveness and use rescue medications appropriately.

Titrating Transdermal Fentanyl

Once we have switched a patient to TDF, how do we titrate the dose up—let's consider both the dose and the timing. Let's start with how quickly we can increase the patch strength. According to the guidelines in the prescribing information for Duragesic® "the initial Duragesic® dose may be increased after 3 days based on the daily dose of supplemental opioid analgesics required by the patient in the second or third day of the initial application. Physicians are advised that it may take up to 6 days after increasing the dose of Duragesic® for the patient to reach equilibrium on the new dose. Therefore, patients should wear a higher dose through two applications before any further increase in dosage is made on the basis of the average daily use of a supplemental analgesic."[4] It makes sense that we cannot gauge the efficacy of the TDF dose within the first 24 hours after initial patch application (or dosage increase) because the serum fentanyl continues to rise during this period. One reference states TDF absorption is 47% complete at 24 hours, 88% complete at 48 hours and 94% complete at 72 hours.[15] Therefore, we should look at average use of the rescue medication on days 2 and 3, and let that guide our titration decision making. Generally speaking, if the patient requires more than three doses of their rescue medication for spontaneous pain in a 24-hour period to achieve good pain control, the patch strength should be increased. Titrating with TDF is challenging and often cumbersome due to the long onset and duration of action. The best rule of thumb is to change the dose when the pain is stable (note I didn't necessary say the pain was *controlled*, but *stable*), but not more quickly than described above.

How much should we increase the patch strength? There are two ways you can do this—first, calculate how much of the rescue opioid the patient was using per day on average, and calculate the conversion to TDF. For example, consider a patient who was switched from an oral opioid regimen to 50 mcg/h TDF with 15 mg MSIR q2h for breakthrough pain. Assume the patient took 4 doses of MSIR on both days 2 and 3, for a total daily dose of 60 mg oral morphine. Half of this is 30 mcg/h, therefore it would be appropriate to increase the TDF to 75 mcg/h. You can also use a rule of thumb to increase the TDF by 25 mcg/h when at lower doses, but increase by 50 mcg/h if the

patient is using a greater amount of rescue medication, their pain is severe, and a 50 mcg/h increase is within reason. For example, you would *not* increase from 25 mcg/h to 75 mcg/h—this would be a 200% increase. We discussed in a previous chapter that we increase by 25–50% for moderate pain, or 50–100% for severe pain. Therefore in the face of more severe pain, you can comfortably increase by up to 100% while not exceeding the absolute increase by 50 mcg/h. For example, a patient on 50 mcg/h TDF who is using around the clock rescue medication and continues complain of pain (assuming an opioid remains the appropriate analgesic) may be increased to 100 mcg/h on day 4. It may also be reasonable to increase the dose of the rescue medication, and observe the patient's response over the next 6 days before considering an additional dosage increase of TDF.

Transdermal fentanyl patches are approved for use for 3 continuous days (72 hours). Clinical practice and research have shown that about 20% of patients may require a shorter application interval to 48 hours.[16] If possible, an increase in the TDF dose is preferred (to be able to maintain the q72h dosing interval), but if the patient consistently has more breakthrough pain during the last 24 hours of each cycle (e.g., using more than 4 doses of rescue opioid), changing to q48h dosing would be appropriate. Dosage intervals less than 48 hours in duration are inappropriate and should not be used in any patient, regardless of the circumstances.

Converting FROM Transdermal Fentanyl—Equivalent Dosing

Occasionally we have a clinical situation where it would be in the patient's best interests to switch *from* TDF to a different opioid or route of administration. Alternately, it may be a formulary consideration driving this decision. In any case, what guidelines do we use to switch off TDF?

The manufacturer's guidelines offer the following recommendations for discontinuation of Duragesic®[4]: "To convert patients to another opioid, remove Duragesic® and titrate the dose of the new analgesic based upon the patient's report of pain until adequate analgesia has been attained. Upon system removal, 17 hours or more are required for a 50% decrease in serum fentanyl concentrations." Can we use our 2 mg oral morphine:1 mcg fentanyl guideline in reverse? Probably, but timing is everything. Let's look at the following case.

CASE 5.3

Switching Off TDF: Timing Considerations

BL is a 52 year old man admitted to your hospice program with a diagnosis of lung cancer; he is receiving 50 mcg/h TDF with MSIR 15 mg po q2h prn breakthrough pain. He is able to swallow tablets and capsules, and TDF is not on your formulary. BL is agreeable to switching to sustained release morphine tablets. You use the 2 mg oral morphine:1 mcg TDF rule, and calculate an approximate total daily dose of oral morphine of 100 mg. But how do we make this switch—how do we time taking off the patch, and beginning the morphine therapy? An important part of answering this question is knowing the rate at which the fentanyl is eliminated from the body after patch removal, as follows:

- 17 hours after patch removal, 50% of fentanyl is eliminated from the body
- 34 hours after patch removal, 75% of fentanyl is eliminated from the body

- 51 hours after patch removal, 87.5% of fentanyl is eliminated from the body
- 68 hours after patch removal, 93.5% of fentanyl is eliminated from the body

Remember, even though fentanyl is a quick-onset, short-acting opioid, when administering by transdermal patch it takes many hours for the drug to completely be absorbed from the site of application (the skin), enter the systemic circulation, be metabolized, and eliminated from the body.

One guideline published in the literature to prevent pain recurrence when switching from TDF to a different opioid/route of administration is as follows[17]:

- Calculate your new opioid regimen. (Note: if you're working with a home-based patient, make *sure* the new opioid is *in* the home before removing the patch; don't gamble on the time of delivery because if you're wrong the patient may end up in a pain crisis!)
- Remove the TDF patch.
- For the first 12 hours after patch removal, use *only* the previously prescribed rescue opioid only for pain that occurs.
- Twelve hours after patch removal, begin with 50% of the calculated scheduled opioid regimen, and continue to offer the rescue opioid as needed.
- Twenty-four hours after patch removal, increase to 100% of the calculated scheduled opioid regimen, and continue to offer the rescue opioid as needed.

In the case of BL, even though we have a good idea that TDF 50 mcg/mL is equivalent to 100 mg/day of oral morphine, you decide to move first to using the oral morphine solution he has in the home on an around the clock basis before ultimately switching him to oral sustained-release morphine tablets. So, let's take a look at how we do this.

After removing the patch, you instruct the patient to wait 12 hours before taking *scheduled* doses of oral morphine, however he is welcome to use the morphine 15 mg every 2 hours as needed for *breakthrough* pain. Based on our rule of thumb of TDF 50 mcg/hour is equivalent to 100 mg oral morphine per day, we determine the 4-hourly dose of oral morphine to be 15 mg. Twelve hours after the patch is removed we instruct BL to take 50% of the calculated dose of morphine, which would be MSIR 7.5 mg po q4h (with rescue opioid still available). After 24 hours BL is instructed to increase to MSIR 15 mg po q4h around the clock. After two days of this regimen, he is switched to sustained-release oral morphine 45 mg po q12h, keeping the MSIR 15 mg po q2h prn breakthrough pain.

Transdermal Fentanyl in Older Adults and Cachectic Patients

As previously discussed, many variables affect the absorption of fentanyl from a transdermal system and age is no exception. By determining the amount of fentanyl left in the transdermal patch after 72 hours, Solassol and colleagues determined that patients > 75 years of age absorbed 50% of fentanyl while patients < 65 years of age absorbed 66% (difference was statistically significant).[18]

As briefly discussed earlier in this chapter, some practitioners who care for patients with advanced illnesses have noticed that cachectic patients occasionally seem to get less relief from TDF than expected.[19] There is no published data to support this finding, but just as we know it makes no sense to actually try to teach a pig to whistle, it would be imprudent to ignore this perceived lack of response. Let's look at a case that illustrates this point.

CASE 5.4

TDF and Cachetic Patients

SW is a 92 year old woman (5'5", 82 lb) admitted to hospice with a diagnosis of failure to thrive. She has a long-standing history of osteoarthritis, affecting her knees, hips and spine. She has painful diabetic neuropathy and a range of general aches and pain. Her pain did not adequately respond to non-opioid analgesics, therefore she was started on morphine 2.5 mg po q4h, over time increasing to 15 mg po q4h. Her pain was fairly well controlled on this regimen, but the morphine made her nauseated. Her physician switched her to 50 mcg/h TDF with good response for about 10 days. When she complained of increased pain, her physician increased the TDF to 75 mcg/h, then to 100 mcg/h 6 days later. Neither dosage increase had any appreciable effect on her pain. You decide to switch her to subcutaneous injections of morphine around the clock. This brings up to our burning question—which strength patch do you base your calculations on? The 50 mcg/h patch, the 75 mcg/h patch or the 100 mcg/h patch?

Since SW did not show a response to either the 75 mcg/h or 100 mcg/h TDF, it would be prudent to base your calculations on the 50 mcg/h patch. Therefore, a 50 mcg/h TDF patch is about equal to 100 mg oral morphine, which is about equal to 33 mg parenteral morphine per day. If we decide to give the SQ injection every 4 hours, this calculates to a 5-mg dose. In addition, you could even get an order for morphine 2.5 or 5 mg SQ every 2 hours as needed for breakthrough pain on top of the regularly scheduled doses of SQ morphine. Using the guidelines discussed above, for the first 12 hours after removing the patch, you would rely solely on the "prn" order; during the next 12 hours you could begin with morphine 2.5 mg SQ every 4 hours (plus the 5 mg q2h prn dose). After 24 hours you would move to your full dose of morphine 5 mg SQ every 4 hours. After 24–48 hours of therapy you will determine if this regimen is sufficient or not.

Importantly, this is not an evidence-based recommendation, it's based more on a violent objection to being thrown in jail for overdosing a LOL (little old lady) on opioids. As we have discussed from the beginning of this book, "Safety First" is our mantra. The second mantra is to make sure the patient has adequate rescue opioid available.

Parenteral Fentanyl

As described in the beginning of the chapter, fentanyl may be administered by several routes of administration. Use of parenteral fentanyl includes IV injection, IV infusion, IM injection (no, no, bad dog!), and SQ injection or infusion. In the hands of skilled practitioners, fentanyl has also been administered epidurally and intrathecally. The remainder of this chapter will be devoted to conversion calculations regarding parenteral fentanyl.

IV Fentanyl

In Chapter 7 we will be discussing advanced opioid therapy including continuous infusions and neuraxial opioid therapy. But since we're talking about fentanyl, let's look at a conversion from oral morphine to a continuous IV (or SQ) fentanyl infusion. As we discussed earlier in the chapter fentanyl is approximately 70–100 times more potent than morphine on a mg-to-mg basis, but there is some debate over the exact

morphine~fentanyl equivalency (of course, life would be too simple if that were not the case!). Let's take a look at a case:

CASE 5.5

Switching from an Oral Opioid to IV Fentanyl

MB is a 48 year old man with a history of a work-related injury resulting in chronic low back pain. His pain is currently being treated with sustained-release morphine 120 mg po q12h with MSIR 30 mg every 4 hours as needed for breakthrough pain (which he takes on average twice a day) with good pain control. He has been admitted to the hospital for back surgery and the surgeon has asked you to convert his oral morphine regimen to a continuous IV fentanyl infusion prior to surgery. No pressure there! Let's take a look at how we do this:

Our first step is to assess the patient's pain; he has told you his current oral morphine regimen controls his pain. Second, we need to calculate his total daily dose of oral morphine. He is getting a total of 300 mg oral morphine per day (120 × 2 plus 30 × 2 = 240 + 60 = 300). Step 3 is the conversion calculation, followed by Step 4, which is individualizing the dose for the patient. Three hundred milligrams a day of oral morphine is equivalent to 100 mg per day of parenteral morphine. If we were going to put him on a continuous IV morphine infusion, we would divide by 24 to get the hourly infusion rate, which would be about 4 mg/hour. Using the equivalency shown in the table in Chapter 1 (10 mg parenteral morphine ~ 0.1 mg parenteral fentanyl), we determine that 4 mg parenteral morphine ~ 0.04 mg fentanyl. We can convert 0.04 mg fentanyl to mcg, which comes out to 40 mcg IV fentanyl/hour. However, as explained in the footnote on that table, many practitioners consider the 1:100 equivalency far too conservative and instead consider 4 mg/hour of IV morphine to be equivalent to 100 mcg/hour of IV fentanyl (a 1:40 equivalency). Using this rule of thumb, MB's *300 mg of oral morphine per day* is approximately equivalent to *100 mg of parenteral morphine per day*, which is equal to *4 mg/hour of parenteral morphine*, which would be equivalent to *100 mcg/hour of IV fentanyl*. So the answer to the question "what hourly dose of parenteral fentanyl is equivalent to 300 mg a day of oral morphine?" is somewhere between 40 mcg/hour and 100 mcg/hour (of IV fentanyl). Based on what we see clinically, the correct answer is closer to the 100 mcg/hour, but if you want to be conservative you could start lower and allow for a generous bolus dose. For example, you could start the patient at 60 mcg/hour of IV fentanyl with a 30 mcg bolus every 15 minutes. Step 5 is closely monitoring your patient; within a few hours you will be able to determine how many doses of breakthrough fentanyl the patient requires, and you can adjust your infusion rate accordingly. Because we are stopping a sustained release oral opioid, we will allow MB to use the fentanyl bolus option for the first 6 hours, then begin the continuous IV infusion of fentanyl.

Converting from Transdermal to IV Fentanyl

As stated earlier, the dose of TDF and IV fentanyl is the same. When you really think about it, transdermal drug delivery technically *is* parenteral drug delivery (it's not enteral)! While you're wrapping your head around that, just recognize that 25 mcg/h of TDF is equivalent to 25 mcg/h of IV fentanyl, and 100 mcg/h of TDF is equivalent to 100 mcg/h of IV fentanyl, and so forth.

So if the dosing equivalency is such so straight forward, why are we taking time to discuss how to switch patients from TDF to IV fentanyl. Funny you should mention "time"—it's all in the timing! As stated earlier, once you remove a TDF patch, it takes about 17 hours to see a 50% decrease in the fentanyl serum concentration. Clearly we don't want to wait 17 hours to start our IV fentanyl, so what is an appropriate way to work out this timing? Most practitioners would use the following technique:

- Remove the TDF patch.
- For the next 6 hours, use "as needed" IV fentanyl for pain management.
- Six hours after TDF patch removal, being an infusion of IV fentanyl at 50% the anticipated dose (in other words, 50% of the TDF patch strength). The "as needed" dose of IV fentanyl is still available.
- Twelve hours after TDF patch removal, increase the IV fentanyl infusion to 100% the anticipated dose (which should be equivalent to the TDF patch strength). The "as needed" dose of IV fentanyl continues to remain available.

On occasion patients receiving transdermal fentanyl experience rapidly escalating pain picture than cannot be managed with a transdermal system. In these cases, the practitioner may chose to switch the patient to intravenous fentanyl. Kornick and colleagues described their protocol for this conversion in patients with acute cancer-related pain.[20] Their protocol was as follows: all transdermal patches were removed from the patient, and a continuous infusion of IV fentanyl was begun at an equivalent hourly rate (1:1, transdermal:IV) at the time of patch removal. A patient-demand bolus of 50–100% of the hourly infusion rate was available every 15–20 minutes. In this published case series, ten patients were switched from transdermal to IV fentanyl, the results of nine were reported. Eight of the nine patients reported pain in excess of 8 on a 0-10 scale on presentation; seven of the nine had a significant decrease in pain intensity at 24 hours. One of the nine patients reported sedation 24 hours after starting IV fentanyl, which resolved by the next day. As discussed by the authors, during the initial hours after the switch from transdermal to IV fentanyl, the patient was actually receiving approximately twice as much fentanyl as the prescribed IV dose due to the continued absorption of fentanyl from the skin depot despite TDF patch removal. In the cases they described, this was useful because all the patients were in pain crisis. This would *not* be appropriate for a patient who was *not* in acute pain crisis.

CASE 5.6

Switching from TDF to Parenteral Fentanyl

AL is a 62 year old man with history of prostate cancer, admitted to the hospital for a course of radiation. To have increased flexibility in treating his pain while hospitalized, the palliative care team has been asked to switch him from his current 50 mcg/h TDF to a continuous IV infusion of fentanyl. AL's pain is currently well controlled on TDF along with a nonsteroidal anti-inflammatory agent. How should we convert AL to a continuous IV fentanyl infusion?

Based on the discussion above, AL is not is pain at this time, so clearly this is not a crisis situation. It would be appropriate to remove the TDF patch, establish IV access and have a 25 mcg fentanyl bolus available every 20 minutes for the first 6 hours. At 6 hours, the

continuous IV infusion of fentanyl should begin at 25 mcg/h, and the bolus option is still available. Twelve hours after TDF patch removal, the IV infusion of fentanyl should be increased to 50 mcg/h, and the bolus options remains in place. Should AL's pain increase or decrease over the next few days, the continuous infusion can be adjusted accordingly.

Converting from IV to Transdermal Fentanyl

When a patient's pain has been stabilized on a continuous infusion of fentanyl, it is common practice to want to switch the patient to a more convenient dosage formulation, such as TDF. Our friends Kornick et al have kindly provided guidance in this area as well![21] They report on a series of adult patients with cancer-related pain who had been treated with continuous infusion fentanyl (with a patient-demand bolus at 50-100% of the hourly infusion rate, available every 15–20 minutes). All patients reported stable and acceptable pain control in the 12 hours prior to conversion to TDF. The protocol they used was to round the effective hourly infusion rate to the closest TDF patch strength, and apply the patch(es). Six hours after TDF patch application, the continuous fentanyl infusion rate was decreased by 50%, and was discontinued 6 hours thereafter. The demand bolus option remained in place at the same dose and lockout interval for at least 24 hours after TDF patch application. Fifteen patients were evaluated in this case series; only one patient reported unsatisfactory pain control at 6 and 12 hours, but acceptable pain control at 18 and 24 hours. Overall, all 15 patients had acceptable pain control using this two-step taper without significant increases in sedation or demand fentanyl bolus use.

CASE 5.7

Switching from Parenteral Fentanyl to TDF

AL, our 62 year old man with prostate cancer from case 5.6, has completed his course of radiation and is ready for discharge home. He is being maintained on a fentanyl continuous infusion at 70 mcg/hour; he has only used his bolus dose (35 mcg) once in the past 24 hours. He would like to resume TDF therapy. How do we handle this transition?

Per the research from Kornick et al., we round the patient's continuous hourly infusion rate to the closest TDF patch strength. The patient is receiving 70 mcg/h, therefore the 75 mcg/h TDF patch seems reasonable. We apply the patch at 8 a.m., and continue the continuous infusion at 70 mcg/h and the bolus dose (35 mcg q20 minutes) remains available to the patient. At 2 p.m. (6 hours later) we reduce his continuous infusion to 35 mcg/h (and continue the demand bolus dose at 35 mcg/h). At 8 p.m. (12 hours after patch application) we discontinue the continuous infusion, but keep the demand bolus dose (35 mcg) available until 8 a.m. day 2 (an additional 12 hours). We will of course be vigilant in monitoring AL for pain control and adverse effects, particularly over-sedation. At 24 hours after patch application if all is well we can discontinue the IV altogether, and order an oral short-acting opioid for breakthrough pain (e.g., MSIR 15 mg po q2h prn pain).

In this chapter we have explored conversions in the land of fentanyl—to and from transdermal fentanyl, and to and from parenteral fentanyl. All that converting to and fro has left me a bit dizzy—hopefully you'll find Table 5-3 helpful. In this summary table you will find all the "pearls" we discussed when converting to and from TDF, and how to adjust the TDF dose. What's not to love about a good cheat sheet?

Table 5-3

Rules of Thumb with Fentanyl Conversions

- **Converting from an oral long-acting opioid to TDF**
  - If patient is not taking oral morphine, convert to oral morphine
  - Using the 2 mg oral morphine/day ~ 1 mcg/h TDF rule, calculate TDF patch strength
  - Advise patient to take one last dose of the oral long-acting opioid at the same time the first TDF patch is applied
  - Increase TDF if necessary in 3 days, and every 6 days thereafter as needed
- **Converting from an around-the-clock oral short-acting opioid to TDF**
  - If patient is not taking oral morphine, convert to oral morphine
  - Using the 2 mg oral morphine/day ~ 1 mcg/h TDF rule, calculate TDF patch strength
  - Advise patient to take two or three scheduled doses of their oral short-acting opioid after TDF patch application: one dose at the time of application, another dose 4 hours later, and if needed, a third dose 4 hours later. Rescue opioid should be available throughout.
  - Increase TDF if necessary in 3 days, and every 6 days thereafter as needed
- **Titrating TDF upward**
  - After initiation of TDF therapy, evaluate use of rescue opioid on days 2 and 3. If patient using more than three doses of rescue opioid, calculate TDD of rescue opioid, and increase TDF patch strength in an equivalent amount.
  - Increase by 25–50 mcg/h, but not to exceed a 100% increase. Also, no dosage increase should exceed 50 mcg/h
    - Increase from 25 mcg/h to 50 mcg/h
    - For patients on 50 mcg/h or higher, increase by 50 mcg/h
- **Converting from TDF to an oral opioid**
  - Based on TDF patch strength, calculate oral morphine equivalent (or other opioid equivalent). If converting to oral morphine, use the 2 mg oral morphine/day ~ 1 mcg/h TDF rule
  - Once the new opioid product is in the patient's home, remove the TDF patch
  - For the first 12 hours after patch removal, use only the previously prescribed rescue opioid
  - Twelve hours after patch removal begin with 50% of the calculated scheduled opioid regimen**;** rescue opioid continues to be available
  - Twenty-four hours after patch removal, increase to 100% of the calculated scheduled opioid regimen; rescue opioid continues to be available
- **Converting from TDF to IV fentanyl**
  - Remove the TDF patch
  - Establish IV access and allow an "as needed" bolus dose of fentanyl
  - Six hours after TDF patch removal, begin 50% of IV fentanyl infusion (which should be 50% of the TDF patch strength); bolus option remains in place
  - Twelve hours after TDF patch removal, increase IV fentanyl infusion to 100% of prescribed amount (which should be equal to the TDF patch strength); bolus option remains in place

Table 5-3 (contd.)

Rules of Thumb with Fentanyl Conversions

- **Conversion from IV fentanyl to TDF**
  - Apply TDF patch in same strength as IV fentanyl infusion.
  - Six hours after application of TDF, reduce IV fentanyl infusion by 50%; bolus option remains in place
  - Twelve hours after application of TDF, discontinue IV fentanyl infusion; bolus option remains in place.
  - Twenty-four hours after application of TDF, discontinue IV fentanyl bolus

PRACTICE PROBLEMS

P5.1: Switching from oral morphine to TDF

TS is a 72 year old man with severe osteoarthritis pain. His prescriber has him on a regimen of morphine oral solution, 20 mg every 4 hours around the clock. When TS remembers to take all six doses of morphine per day his pain is very well controlled. Unfortunately, when he forgets to take doses he ends up in pain crisis. His prescriber asks your help in converting TS to TDF. What do you recommend, and specifically how should the switch be timed?

P5.2: Switching from oral long-acting oxycodone to TDF

HH is a 62 year old woman with chronic low back pain, currently taking OxyContin 40 mg po q12h with OxyIR 10 mg every 2 hours (takes about 4 times per day). This reduces HH's pain to about a 4 on a 0–10 scale. Unfortunately, HH complains that she cannot afford the OxyContin tablets, and she would like to switch to generic TDF. What do you recommend?

P5.3: Switching from TDF to oral morphine

DW is a 48 year old man who just moved to the area for a new job. He has a 10-year history of chronic low back pain for which he receives 100 mcg/h TDF. Unfortunately his new prescription plan does not cover TDF and he has been referred to you for conversion to oral morphine. What do you recommend?

P5.4: Switching from TDF to IV fentanyl

TJ is a 58 year old man with end-stage lung cancer, who has been admitted to your inpatient hospice unit for uncontrolled pain. He is currently receiving 75 mcg/h TDF with MSIR 15 mg po q2h for breakthrough pain. He rates his pain as a 9 out of 10, where it has been for the past 24 hours. He has taken several doses of the MSIR but tells you "that stuff doesn't work, so I quit taking it." You would like to switch him to a continuous IV infusion of fentanyl. What is your dosing strategy?

P5.5: Switching from IV fentanyl to TDF

TJ, the 58 year old man with end-stage lung cancer described in case P5.4, was admitted and switched to a continuous fentanyl infusion. Several days later his pain is very well controlled on 120 mcg/h of fentanyl with a 40 mcg bolus every 15 minutes

as needed for breakthrough pain. He has used 4 doses of the rescue fentanyl over the past 24 hours. He would now like to be transitioned back to TDF so he can return home. What do you recommend and how do you make a smooth transition?

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ADDITIONAL SUGGESTED READING

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SOLUTIONS TO PRACTICE PROBLEMS

P5.1: Importantly, TS's pain is well controlled when he takes all the morphine prescribed for him, which is 120 mg per day (morphine 20 mg po q4h around the clock). Using our 2 mg oral morphine:1 mcg TDF guideline, this works out to be 60 mcg/h TDF. Our decision at this point is to either round up to 75 mcg/h TDF or down to 50 mcg/h TDF. Given TS's age and the fact that his pain was very well controlled (when he took the morphine), it would be appropriate to round down to 50 mcg/h TDF. Specific timing would be as follows:

8 a.m.—apply 50 mcg/h TDF patch
8 a.m.—take oral morphine 20 mg
12:00 p.m.—take oral morphine 20 mg
Offer oral morphine 20 mg q2h prn from 8 a.m. onward

P5.2: First, we calculate HH's total daily dose of oral oxycodone. OxyContin 40 mg po q12h = 80; plus OxyIR 10 mg × 4 doses per day = 40 mg, for a TDD of 120 mg oral oxycodone. Using one of our ratio equations, we determine that 120 mg oral oxycodone is approximately equivalent to 180 mg oral morphine. Using our 2 mg oral morphine:1 mcg TDF rule of thumb, this works out to be 90 mcg/h TDF. Therefore we must either round down to 75 mcg/h TDF or increase to 100 mcg/h TDF. Since HH's pain control could be improved, it would be appropriate to increase to 100 mcg/h TDF. For breakthrough we can continue to use the OxyIR, giving 10-15% of the TDD (120 mg oxycodone)—15 mg every 2 hours as needed for breakthrough pain would be appropriate. HH should take one last OxyContin tablet when she applies the 100 mcg/h TDF patch, and use her rescue opioid as needed.

P5.3: DW is using a 100 mcg/h TDF patch, which is approximately equivalent to 200 mg per day of oral morphine. If we gave the oral morphine using the short-acting formulation this would be 30 mg every 4 hours, and a rescue dose of 20 mg every 2 hours as needed. We recommend the following conversion plan for DW:

- Remove 100 mcg/h TDF patch at 8 a.m.
- For the next 12 hours use short-acting morphine 20 mg every 2 hours as needed for pain
- For the next 12 hours (hours 13–24) patient should take oral morphine 15 mg every 4 hours, and an extra 15 mg as needed every 2 hours
- Starting at 24 hours take oral morphine 30 mg every 4 hours around the clock, and an extra 15 mg as needed every 2 hours

After 3 days on oral morphine 30 mg every 4 hours around the clock, he had good pain control (rated as a 3 or 4 on a 0–10 scale) and did not need any rescue doses. He was switched to MS Contin 100 mg q12h

P5.4: As was described in the Kornick study, because TJ is in pain crisis, it would be appropriate to remove the 75 mcg/h TDF patch, and immediately begin a continuous IV infusion of fentanyl at 75 mcg/h. The patient should also have a demand bolus available at 50–100% of the continuous infusion hourly rate, therefore it would be appropriate to offer 40 mcg every 20 minutes as needed. Of course the palliative care practitioners will have to closely monitor TJ for sedation, as well as pain control and other adverse effects. TJ will also have to be carefully assessed to determine why he is having a pain crisis (e.g., pathological fracture, etc.).

P5.5: TJ's pain is well controlled on 120 mcg/h of IV fentanyl, therefore we will apply one 100 mcg TDF and one 25 mcg/h TDF patch at 8 a.m.. We will continue the infusion at 120 mcg/h and keep the bolus option in place. At 2 pm (6 hours after patch application) we reduce the continuous infusion to 60 mcg/h, but keep the same bolus option in place. At 8 pm (12 hours after patch application) we discontinue the continuous infusion, but keep the same bolus option in place. At 8 a.m. on Day 2 we discontinue the bolus option and convert TJ to an oral short-action opioid for breakthrough pain, such as MSIR 30 mg po q2h prn pain.