CHAPTER 5

# Transdermal and Parenteral Fentanyl Dosage Calculations and Conversions

## INTRODUCTION

Fentanyl is a synthetic phenylpiperidine derivative with pharmacologic properties similar to morphine, hydromorphone, oxycodone, and other opioids. Fentanyl has potent mu-opioid receptor activity and some activity at the δ- and κ-opioid receptors as well. Important differences about fentanyl include its high degree of potency (about 75–100 times more potent than morphine on an mg-to-mg basis), and high lipid solubility (far greater than morphine). Fentanyl has a large volume of distribution (approximately 6 L/kg) and is rapidly distributed from the plasma into highly vascularized compartments and eventually redistributed to muscle and fat tissue.[1] The lipophilic nature of fentanyl also facilitates rapid diffusion across the blood-brain barrier, resulting in a quick onset of action once the drug is absorbed from the administration site.[1] The transfer half-life from the systemic circulation to the central nervous system (CNS) is 4.7 to 6.6 minutes.[2]

### OBJECTIVES

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

1. Describe the pharmacokinetics of fentanyl, and variables that can influence transdermal and parenteral 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 parenteral fentanyl and transdermal fentanyl.

Practitioners commonly think of parenteral fentanyl as fast onset and short acting and morphine as slower onset and longer acting, but actually fentanyl and morphine have similar elimination half-lives (2–4 hours for morphine and 3–7 hours for fentanyl).[3] Fentanyl, as described above, is a *fast-in, fast-out* drug, crossing the blood-brain barrier quickly in a bidirectional fashion. Morphine, however, is described as a *slow-in, slow-out* drug when crossing the blood-brain barrier.[3]

As described in the Equianalgesic Opioid Dosing table in Chapter 1, when fentanyl is administered as a single intravenous (IV) bolus, it has a redistribution-limited short duration of action. However, with prolonged exposure to fentanyl (multiple boluses or continuous infusion), elimination is clearance limited.[4] With repeated doses or continuous infusion, the duration of effect of fentanyl is longer

than that seen with a single IV bolus due to accumulation in the muscle and fat tissue compartments.[1] Fentanyl is extensively metabolized by the cytochrome P450 isoenzyme system, primarily by the CYP3A4 enzyme.[4] Predictably, fentanyl is subject to altered serum concentrations when co-administered with a CYP3A4 enzyme inducer or inhibitor.

Because fentanyl is a small and highly lipophilic molecule with low ionization and has the ability to pass through cellular barriers reaching the capillary bed, it is well suited for absorption across biological membranes (e.g., transdermal and transmucosal), demonstrating bioavailability ranging from 50% to 90%.[1,3]

***Because of these properties, 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 IV injection, IV infusion, subcutaneous (sub-Q) 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 pre-operatively, intra-operatively, 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*—**Transdermal fentanyl patches (TDF; also referred to as *fentanyl transdermal system*) have been available for many years; this formulation relies on passive diffusion [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 pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment.
- ***Buccal* and *transmucosal*—**As discussed in Chapter 4, these are immediate-release dosage forms approved to treat breakthrough pain in cancer patients.
- ***Fentanyl iontophoretic transdermal system*—**This system had been developed for the short-term management of acute postoperative pain in adults and was briefly on the market. The drug was delivered on patient demand, with an electrical charge driving the drug into the skin. The manufacturer voluntarily withdrew this product from the market in June 2017.[5]

Lötsch and colleagues provide an excellent diagram (Figure 5-1) and explanation of the differences in the sites of fentanyl absorption relative to the various routes of nonparenteral fentanyl administration. They state, "The actions of fentanyl are related to its concentrations at opioid receptors expressed within its main effect site, the CNS. Except for intranasal administration, whereby fentanyl is also directly delivered to the CNS, the extent and time course of its effects are a function of the time course of its plasma concentrations, $C_p(t)$."[2] They conclude by pointing out that the plasma concentration of fentanyl is influenced by the rate of fentanyl influx and the rate of fentanyl disposition (metabolism and excretion).

This chapter will focus on conversion calculations involving switching to and from TDF, and conversion calculations involving parenteral fentanyl.