



PALLIATIVE CARE CASE OF THE MONTH

Pearls and Pitfalls of Transdermal Fentanyl Administration Scott Freeman, MD

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Case: Mrs. G. is a 62 year old woman with a past medical history significant for multiple myeloma with vertebral compression fractures status post kyphoplasty and status post peripheral stem cell transplant, chemotherapy and radiation therapy who suffers from chronic low back pain. A regimen had been devised in the outpatient clinic consisting of transdermal Fentanyl 125mcg/hr changed every 72hrs and Dilaudid 6mg PO every 4hrs as needed. The patient reported adequate pain relief and had been requiring only 2 to 3 doses of dilaudid per day. She was then admitted to the hospital for her second peripheral stem cell transplant. The palliative care service was consulted for symptom management and, although her pain was well-controlled, we were asked to discontinue the Fentanyl patch and create another regimen out of concern for excessive transdermal absorption in the event she developed fever during the course of her transplant.

Discussion: Fentanyl is a synthetic mu-opioid receptor agonist which is available for delivery via many routes including intravenous, buccal, sublingual, intranasal, and transdermal. Fentanyl is a lipophilic (highly lipid soluble) drug, unlike morphine, hydromorphone, or oxycodone. This quality, along with its relatively low molecular weight, is what enables its use via the transdermal route and allows rapid diffusion across the blood-brain barrier producing rapid onset of action. Transdermal Fentanyl represented a novel opiate delivery system when it earned FDA approval in 1991 and, consequently, there was a great deal of concern at that time about its safety and the nature of its pharmacokinetics. It is currently approved for use for treatment of moderate to severe **chronic pain in opioid tolerant patients.**

It should not be used for acute or intermittent pain or by patients who are using less than 60mg of oral morphine daily or the equivalent.

The Fentanyl transdermal system is a patch which delivers a continuous dose of the medication such that it only needs to be changed every 72 hours. There are 5 different patch dosages available: 12 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr, and 100 mcg/hr. Dose delivery is dependent on the surface area of the patch, so higher dose patches are larger than smaller dose patches. The patch needs to be applied to a flat, intact skin surface – usually the chest, upper arm, or back. Excessive hair surrounding these areas can be cut rather than shaved (alterations in skin integrity caused by shaving could theoretically increase the rate of drug delivery). The drug is absorbed through the skin creating a cutaneous depot of Fentanyl in the stratum corneum layer of the skin. By passive diffusion, the drug then makes its way from the depot deeper to the microcirculation in the dermis to the systemic circulation. The rate of diffusion and subsequent absorption is, in part, regulated by a rate-limiting membrane built into the backing of the patch to ensure continuous and consistent dose release from the patch's drug reservoir.

Serum fentanyl concentrations increase gradually after patch application and begin to reach analgesic doses after about 12 hours and peak concentrations at about 36 hours. Steady state may take from 3 to 6 days to be achieved. Given this, it is important to make changes to transdermal fentanyl dosing no sooner than 3 days after initiation or a previous dosage change. After removal, the serum drug level drops by one-half after about 17 hours, a fact that is important to keep in mind when changing to another long-acting agent.

Personal details in the case published have been altered to protect patient privacy.

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Like many other medications, great patient to patient variability in drug delivery has been observed with Fentanyl. There are many additional factors that are important to be mindful of in the management of transdermal fentanyl. One concern, expressed by the primary team in the case above, is about the potential variability in transdermal absorption with alterations in body temperature. A physicochemical model constructed by Gupta et al. showed increased permeation with increased temperature such that increasing the body temperature by 3 degrees Celsius translated to an increase in serum fentanyl concentration of 25%. Of note, this data is largely theoretical and there are no published case reports of clinical overdose due to fever. Additional studies revealed that the external application of heat to the patch (e.g. heating pad, warming blanket, sauna, hot tubs, sunbathing, and even strenuous physical exertion) may result in a 3-fold increase in serum concentrations. There have been case reports of associated respiratory depression in patients due to heating pads, warming blankets, sunbathing and strenuous physical exertion so these potential dangers should be discussed with patients.

Another concern is that the patch is less effective in cachectic patients. A study in 2009 by Heiskanen et al showed significantly lower serum concentrations of fentanyl in cachectic patients using the patch versus their normal BMI counterparts. They did not, however, establish that the analgesic effect was diminished in those same patients as there is no proven correlation between concentration and level of analgesia. If cachectic patients do have some degree of impaired absorption, this may simply mean that a higher dose will be needed. Other issues complicating the use of the Fentanyl patch include concomitant use with drugs that act as cytochrome P450 3A4 system inhibitors (e.g. fluconazole, clarithromycin, amiodarone, diltiazem, ritonavir, etc.) which may increase the serum levels of fentanyl.

Only one case report surfaced on literature review regarding this interaction in which a patient was thought to have developed delirium due to co-administration of diltiazem and transdermal fentanyl. There are many variables to keep in mind to ensure safety and efficacy in patients using transdermal Fentanyl. Some of these concerns seem to be largely theoretical or anecdotal with little supporting clinical evidence and, thus, closer monitoring may be advised rather than avoidance of or switching from the Fentanyl patch.

Resolution of the case: As per the request of the primary team, Mrs. G. was transitioned from her Fentanyl patch to and IV Fentanyl infusion. This was done by removing the patch and starting the IV continuous infusion in its place. Given the time it takes for the transdermal fentanyl to clear, her IV continuous infusion was started 6 hours after removal of the patch at the same rate (150mcg per hour) and she was monitored closely and did quite well. Another approach in the literature suggests (1) removal of the patch, (2) use only prn pain medications for 6 hours following removal (3) 6 hours after removal, start the IV infusion at half the patch dose (in this case 75mcg per hour) with prn dosing available; (4) 12 hours after removal, increase to 100% of the dose (150mcg per hour). The patient did well and ultimately was transitioned back to the Fentanyl patch successfully prior to discharge.

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