Class: Strong opioid analgesic.

Indications: Moderate–severe chronic (persistent, long-term) pain, including †AIDS,[1] †morphine intolerance.[2]

Contra-indications: Acute (transient, intermittent or short-term) pain, e.g. postoperative, and in those who need rapid dose titration for severe uncontrolled pain.

Pharmacology

Transdermal (TD) fentanyl is used in the management of chronic severe pain,[3-5] particularly in cancer.[6-13] Fentanyl (*like* **morphine**) is a strong μ-opioid receptor agonist. Because of its high lipophilicity, fentanyl (*unlike* **morphine**) is sequestrated in body fats, including epidural fat and the white matter of the CNS.[14,15] This means that fentanyl given by any route (including spinally) acts supraspinally mainly in the thalamus (white matter). Any effect in the dorsal horn (grey matter) is probably minimal.[14] This may account for the clinical observation that patients with poor pain relief despite using very high doses (e.g. 600microgram/h TD) sometimes obtain good relief with relatively smaller doses of **morphine**, e.g. 10–20mg SC.[16] On the other hand, the lipophilic nature of fentanyl probably accounts for its reduced tendency to cause constipation.[17]

Two different patch formulations are currently available:

- *reservoir* patch (Duragesic®), the fentanyl is contained within a reservoir, and the release of fentanyl is controlled by a rate-limiting membrane
- *matrix* patch, the fentanyl is evenly distributed throughout a drug-in-adhesive matrix, and the release of fentanyl is controlled by the physical characteristics of the matrix.

Absorption of the fentanyl through the skin and into the systemic circulation is influenced by both the stratum corneum of the skin and blood flow. Thus, if the skin is warm and vasodilated, the rate of asbsorption will be increased.

The *reservoir* and *matrix* patches are bio-equivalent with similar pharmacokinetic profiles, and patients can be switched from one to the other with no loss of efficacy or increase in undesirable effects.[18-20] Steady-state plasma concentrations of fentanyl are generally achieved after 36–48h[1] but, according to the manufacturer, this may sometimes be achieved only after 9–12 days. Elimination principally involves biotransformation in the liver by CYP3A4 to inactive norfentanyl which is excreted in the urine. Less than 7% is excreted unchanged. If effective analgesia does not last for 3 days, the correct response is to increase the patch strength. Even so, a small percentage of patients do best if the patch is changed every 2 days.[21] The manufacturer recommends a dose conversion ratio for **morphine** and fentanyl of 150:1. However, several RCTs support a smaller ratio, ranging between 70–125:1. Consequently, *HPCFusa* has opted for a ratio of 100:1; this is also the ratio used in the PI in Germany.[22]

TD fentanyl is less constipating than **morphine**.[6,21,23,24] Thus, when converting from **morphine** to fentanyl, the dose of laxative should be halved and subsequently adjusted according to need. Some patients experience withdrawal symptoms (e.g. diarrhea, colic, nausea, sweating, restlessness) when changed from PO **morphine** to TD fentanyl despite satisfactory pain relief. This is probably related to differences

between the two opioids in relation to their relative impact on peripheral and central μ-opioid receptors. Such symptoms are easily treatable by using rescue doses of **morphine** until they resolve after a few days. TD fentanyl can be continued until the death of the patient, and the dose varied as necessary.
Bio-availability 92%.
Onset of action 3–23h.[25]
Time to peak plasma concentration 24–72h.
Plasma halflife 13–22h (after removal of a patch).[26]
Duration of action 72h; for some patients, 48h.[27]

Cautions

In 2005, after reports of serious overdoses and deaths, the FDA issued a safety warning about the use of TD fentanyl. Factors which contributed to the undesirable drug events included:

- lack of appreciation that fentanyl is a strong opioid analgesic
- inappropriate use for short-term, intermittent or postoperative pain in patients who had not previously been receiving a strong opioid
- lack of patient education regarding directions for safe use, storage and disposal
- lack of awareness of the signs of an overdose and when to seek attention
- lack of awareness that the rate of absorption of fentanyl may be increased if the skin under the patch becomes vasodilated, e.g. in febrile patients, or by an external heat source, e.g. electric blanket, heat lamps, saunas, hot tubs
- lack of awareness of drug interactions that can increase fentanyl levels.

Fentanyl is metabolized by CYP3A4; fentanyl levels may be increased by potent CYP3A4 inhibitors (e.g. **clarithromycin**, **itraconazole**, **ketoconazole**, **nefazodone**, **nelfinavir**, **ritonavir**, **troleandomycin**). The reservoir patches should not be cut because damage to the rate-controlling membrane can lead to a rapid release of fentanyl and overdose.

Undesirable effects
For full list, see manufacturer's PI.
Less constipating than equivalent doses of **morphine**,[6,21,23,24] and may be less emetogenic. Also see Strong opioids, p.000.

Dose and use

The use of TD fentanyl patches is summarized in the Guidelines, p.000. These and the comments in this section are based on a dose conversion ratio with **morphine** of 1:100. Prescribers using the manufacturer's preferred ratio of 1:150 should follow the Dose Conversion Guidelines in the PI.
Note: under no circumstances should a reservoir patch be cut in an attempt to reduce the dose. Leakage from the cut reservoir could result in either the patient receiving minimal or no fentanyl, or, alternatively, an overdose from the rapid absorption of fentanyl through the surrounding skin.

Reservoir and matrix patches are bio-equivalent. The matrix patch is thinner (because there is no reservoir), and smaller (for equal strengths, the matrix patch is

>1/3 smaller). Consequently, to avoid confusing the patients and carers, it is generally better if one formulation is prescribed consistently for any one individual.

The PI stresses that TD fentanyl should be commenced only in patients who have been receiving strong opioids in a dose *more or less* equivalent to a 25microgram/h patch for ≥1 week, such as:

- morphine 60mg/day PO
- oxycodone 30mg/day PO
- hydromorphone 8mg/day PO.

However, TD fentanyl has been used satisfactorily as *first-choice strong opioid* in, for example, patients with severe dysphagia, renal failure or who are living in social circumstances where there is a high risk of diversion and tablet misuse. (Note: it is possible to extract fentanyl, particularly from the *reservoir* patch, and misuse it.)

TD fentanyl is also used in *totally opioid-naïve patients* at centers which skip Step 2 of the WHO analgesic ladder.[28-30] However, fentanyl 25microgram/h (600microgram/24h) is equivalent to **morphine** 60mg PO, and is more than some patients need. Thus, undesirable effects are more frequent in strong opioid-naïve patients. In one study, undesirable effects resulted in 2%, 6% and 8% of patients discontinuing TD fentanyl depending on whether they had previously been receiving strong opioids, weak opioids or non-opioids respectively.[30]

Although not recommended by the manufacturer, when using the 25microgram/h patch to initiate TD treatment, some practitioners cover part of the underside of the patch (*reservoir*) or cut patches (*matrix*) so as to decrease the initial dose. These practices have become unnecessary since the introduction of the 12microgram/h matrix patch, even though it is labeled only for *dose titration* between 25 and 75microgram/h patches, i.e. 25→ 37→ 50→ 62→75microgram/h.

It should be noted that, unless patients have been taking several rescue doses per day of **morphine** (or other strong opioid) for breakthrough pain, escalating in one step from 25–50microgram/h (a dose increase of 100%) can cause a marked (but temporary) increase in undesirable effects.[31]

It is important to give adequate rescue doses of **morphine** (see Guidelines, p.000) or other strong opioid, or **transmucosal fentanyl** (see p.000). Adjusting the patch strength on a daily basis is not recommended.[32] With inpatients, a Fentanyl patch chart is generally helpful.

Supply

All TD fentanyl patches are Schedule II controlled substances.

Fentanyl transdermal (generic)

Reservoir patches (for 3 days) 25microgram/h, 1 = $15 (AWP), 50microgram/h, 1 = $27 (AWP), 75microgram/h, 1 = $41 (AWP), 100microgram/h, 1 = $54 (AWP).

Matrix patches (for 3 days) 25microgram/h, 1 = $15 (AWP); 50microgram/h, 1 = $27 (AWP); 75microgram/h, 1 = $41 (AWP); 100microgram/h, 1 = $54 (AWP).

Duragesic® (Janssen Pharmaceutica)

Reservoir patches (for 3 days) 12.5microgram/h *labeled as Duragesic-12*, 1 = $14 (AWP); 25microgram/h, 1 = $16 (AWP); 50microgram/h, 1 = $29 (AWP); 75microgram/h, 1 = $43 (AWP); 100microgram/h, 1 = $57 (AWP).

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HPCFusa Guidelines Use of transdermal fentanyl patches

These guidelines differ from the USA PI recommendations in that, instead of using a dose conversion ratio for morphine to fentanyl of 150:1, they use 100:1 (as in the German PI); they also include recommendations from the UK PI.
Note: pain not relieved by morphine will generally not be relieved by fentanyl. If in doubt, seek specialist advice before prescribing TD fentanyl.

1 Indications for using TD fentanyl instead of morphine include:
- intolerable undesirable effects with morphine, e.g. nausea and vomiting, constipation, hallucinations, dysphagia
- renal failure (fentanyl has no active metabolite)
- 'tablet phobia' or poor compliance with oral medication
- high risk of tablet misuse/diversion.

2 TD fentanyl is *contra-indicated* in patients with acute (short-term) pain and in those who need rapid dose titration for severe uncontrolled pain. TD fentanyl is best reserved for patients already on a stable dose of morphine (or other opioid analgesic) for ≥1 week.

3 TD fentanyl patches are available in 5 strengths: 12, 25, 50, 75 and 100microgram/h for 3 days. Although labeled only as an aid to titration, there is no pharmacological reason for not using the 12microgram/h patch as the starting dose for TD fentanyl.

4 Use the following table to decide a safe starting dose for TD fentanyl, and an appropriate rescue dose. Patients taking a weak opioid should start on 12microgram/h.

5 For patients taking a dose of morphine that is not the exact equivalent of a fentanyl patch, it will be necessary to opt for a patch which is either slightly more or slightly less than the morphine dose. Thus, if the patient still has pain, round up to a higher patch strength; if pain-free and frail, round down.

Table Comparative doses of PO morphine and TD fentanyl (based on dose ratio 100:1)

Morphine PO		Morphine SC/IV		Fentanyl patch	
mg/24h	p.r.n mg[a]	mg/24h[b]	p.r.n mg[a]	microgram/h	mg/24h
30	5	15	2.5	12	0.3
60	10	30	5	25	0.6
120	20	60	10	50	1.2
180	30	90	15	75	1.8
240	40	120	20	100[c]	2.4

a. using traditional 1/6 of total daily dose as p.r.n. dose
b. assuming potency ratio of morphine SC/IV to PO of 2:1
c. for combinations of patches, add the p.r.n. doses together, e.g. 100 + 75microgram/h patches = 20 + 15mg morphine SC/IV = 35mg morphine SC/IV, but can round up to 40mg or down to 30mg for convenience.

6 Apply the patch to dry, non-inflamed, non-irradiated, hairless skin on the upper arm or trunk; body hair may be clipped but not shaved. If the skin is washed beforehand, use only water; *avoid soaps, oils or lotions*. Press patch firmly in place for at least 30 seconds. Micropore® or Tegaderm® may be necessary to ensure adherence.

7 Systemic analgesic concentrations are generally reached within 12h. If converting from:
- *4-hourly PO morphine*, give regular doses for the first 12h after applying the patch
- *12-hourly SR morphine*, apply the patch and the final SR dose at the same time
- *24-hourly SR morphine*, apply the patch 12h after the final SR dose
- *CSCI/CIVI*, continue the syringe driver for about 12h after applying the patch.

8 Steady-state plasma concentrations of fentanyl are generally achieved after 36–48h; the patient should use p.r.n. doses liberally during the first 3 days, particularly during the first 24h. Safe rescue doses of PO morphine are given in the table above.

9 After 48h, if a patient continues to need 2 or more rescue doses of morphine a day, the strength of the next patch to be applied should be increased by 12–25microgram/h. (Note: when using the manufacturer's recommended starting doses, about 50% of patients need to increase the patch strength after the first 3 days.)

10 About 10% of patients experience opioid withdrawal symptoms when changed from morphine to TD fentanyl. These manifest with symptoms like gastric flu and last for a few days; p.r.n. doses of morphine will relieve troublesome symptoms.

11 Fentanyl is less constipating than morphine; halve the dose of laxatives when starting fentanyl and re-titrate. Some patients develop diarrhea; if troublesome, control with rescue doses of morphine, and completely stop laxatives.

12 Fentanyl probably causes less nausea and vomiting than morphine but, if necessary, prescribe haloperidol 1.5mg stat & h.s.

13 In febrile patients, the rate of absorption of fentanyl increases, and occasionally causes toxicity, principally drowsiness. Absorption may also be enhanced by an external heat source over the patch, e.g. electric blanket or hot-water bottle; patients should be warned about this. Patients may shower with a patch but should not soak in a hot bath.

14 Remove patches after 72h; change the position of the new patches so as to rest the underlying skin for 3–6 days.

15 A reservoir of fentanyl cumulates in the body, and significant blood levels persist for at least 24h after discontinuing TD fentanyl.

16 TD fentanyl is unsatisfactory in <5% of patients. However, discontinuation is more common when TD fentanyl is used in strong opioid-naïve patients.

17 In moribund patients, continue TD fentanyl and give additional SC morphine p.r.n. (see Table above). If >2 p.r.n. doses are required/24h, give morphine by CSCI, starting with a dose equal to the sum of the p.r.n. doses over the preceding 24h. If necessary, adjust the p.r.n. dose taking into account the total opioid dose (i.e. TD fentanyl + CSCI morphine).

18 Used patches still contain fentanyl; after removal, fold the patch with the adhesive side inwards and discard in a sharps container (hospital) or flushed down the toilet (home), and wash hands. Ultimately, any unused patches should be returned to a pharmacy.