

## Palliative Medicine Doctors Meeting

### The Use of Subcutaneous and Sublingual Fentanyl in symptom management : Case Series and Literature Review

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#### Case Scenario

*Mr. Ma, a 63 year- old widower with four children, was previously chair to bed bound with dependent daily living due to old stroke with left hemiparesis. He was diagnosed to have carcinoma of sigmoid colon and Hartman's operation with ileocecal resection performed. A large ulcerative growth was noted at mid-sigmoid colon invading parietal peritoneum and retroperitoneal tissue. Seven months later he presented with abdominal pain and bilateral hydronephrosis was detected. CT scan showed local pelvic recurrence and widespread dissemination, with both ureters obstructed, multiple intraperitoneal masses, ascites, lung secondaries, and abdominal scar metastases. He was put on sublingual Buprenorphine 0.2 mg q8H plus oral morphine 5 mg q4h by the surgical team and was discharged home. He was admitted to our palliative care ward for persistent moderate pain over the masses over abdominal scar with Pain score 2 (out of 4) He was drowsy on admission with a short attention span, and was only able to give 'Yes' or 'No' answers. Renal functions were grossly abnormal with serum urea concentration of 48 mmol/L, and serum creatinine concentration of 1130 umol/L. Continuous subcutaneous fentanyl 200 mcg/day was started for pain control due to excessive drowsiness while on morphine, inadequate pain control and acute renal failure. The dose was increased from 200 to 500 mcg/day over 1 week. His conscious state improved and he was able to communicate with family and to participate in family ceremony. Satisfactory pain control was achieved on Day 3 with pain score of 1. His condition then continued to deteriorate with development of acidotic breathing. He subsequently died one week after subcutaneous fentanyl was commenced.*

The above case demonstrated the problem of using morphine in patients with abnormal renal functions, and the potential role of subcutaneous fentanyl in such cases. Morphine is metabolized in the liver to morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G). M6G acts on mu receptors and has analgesic property and accounts for morphine side effects like respiratory suppression, neuropsychiatric symptoms, and constipation. M6G and M3G are excreted by the kidneys. Opioid intoxication in patients with renal failure was associated with the raised M6G level.<sup>1</sup> Alternative opioid, subcutaneous fentanyl is considered in patients requiring parenteral opioid treatment in situations when morphine is inappropriate.

#### Case Review

A retrospective case notes review of the use of subcutaneous fentanyl infusion and sublingual fentanyl in liquid form was reported. In seven patients, various problems of using morphine were encountered, 6 patients were shifted to continuous subcutaneous fentanyl infusion and 1 patient shifted to sublingual fentanyl. The following table summarizes the features of these seven cases.

Table 1: Case characteristics of use of subcutaneous or sublingual Fentanyl in Haven of Hope Hospital in 2002

Patient	Sex And Age	Cancer	Symptoms requiring opioid	Reason for using Fentanyl	Route CSCI SL	Daily Dose (mcg)	Duration (Days)	Outcome And Side Effects
1	F 52	Colon	Pain	Deteriorating RFT, Shift from fentanyl patch for easy titration	CSCI	300-400	6	Pain score fell from 2 to 1; remained conscious till day before death
2	F55	Colon	Pain	Fluctuating RFT; Methadone overdose	CSCI	150-450	15	Pain score =1 Regained consciousness
3	M72	Chondrosarcoma	Dyspnea	Fear about morphine; morphine refusal	SL	150-300	3	Dyspnea Score fell from 3 to 1; Conscious till death
4	M65	Liver	Dyspnea	Deteriorating RFT to advanced renal failure	CSCI	100-250	2	Improvement in dyspnea described as fair and temporary only
5	M93	Stomach	Dyspnea	Rapid deteriorating RFT	CSCI	100-300	3	Effects described as good
6	M63	Colon	Pain	Drowsiness with morphine; Acute renal failure	CSCI	200-500	8	Pain score fell from 2 to 1; Conscious state improved
7	M59	Colon	Pain and Dyspnea	Deteriorating RFT Methadone ineffective	CSCI	300-700	5	Pain score fell from 2 to 1; Remained conscious

(SL: Sublingual; CSCI: Continuous subcutaneous infusion)

In 6 out of 7 patients, there were rapidly deteriorating or fluctuating renal functions, making morphine titration difficult. The effects of fentanyl for symptom control were reported to be satisfactory in most cases. In one case with acute onset of dyspnea, the effect of subcutaneous fentanyl was reported to be fair only. In all patients, no significant side effects like constipation, over-sedation, confusion or respiratory suppression were reported. Overall, in situations where there was need for an alternative opioid, the use of either continuous subcutaneous fentanyl infusion or sublingual fentanyl (in liquid form) was promising, with satisfactory symptom control and acceptable side effect profile.

## Discussion

In the 1950s, Paul Janssen, of Netherlands first synthesized fentanyl as a more potent and shorter acting opioid than morphine for surgical anesthesia. Since then, intravenous fentanyl has been used for over 30 years for its controllable anesthetic and analgesic properties. It has not been used for the management of cancer pain till the 1980s.

Fentanyl is a phenylpiperidine derivative with high potency and is highly lipophilic. It rapidly diffuses across membranes and into the cerebrospinal fluid, the placenta and breast milk. It is extensively distributed within tissues and it acts on mu opioid receptors.

Its pharmacokinetics are not affected significantly in surgical patients with cirrhosis of liver,<sup>2</sup> and has not been associated with clinical problems when given to patients with liver dysfunction. It has no active or toxic metabolites and had not been associated with clinical problems when given to patients with renal dysfunction.<sup>3</sup> This property makes fentanyl a better choice than morphine for patients with renal failure.

Fentanyl has been used as an analgesic, an adjunct to general anesthesia, an anesthetic agent for induction and maintenance, and a respiratory depressant in mechanical ventilation. It can be given intravenously, transdermally as patch, subcutaneously as injection or infusion, transmucosally via the sublingual or nasal mucosa, inhalationally, epidurally and intrathecally.

### *Intravenous and subcutaneous fentanyl*

Intravenous fentanyl is fast acting with peak action at 1.35 minutes. It has a elimination half-life of 6.1 hours. There are two phases of systemic clearance: the initial redistribution into body tissues, and the subsequent hepatic and renal drug elimination. It is metabolized primarily in the liver while

6% is excreted unchanged in kidney. Its metabolites (norfentanyl, 4-N-anilino piperidine, propionic acid) are not pharmacologically active. Intravenous fentanyl is primarily used for anesthesia. It takes 14 hours for transdermal fentanyl to achieve clinically relevant plasma levels in first dose. The mean bioavailability is 0.92 and the elimination half-life is about 17 hours. It is primarily used for chronic stable cancer pain.

### ***Subcutaneous Fentanyl infusion***

There are few pharmacokinetics study for subcutaneous fentanyl infusion. Whether its pharmacokinetics can be implied from intravenous fentanyl is not certain. In a pharmacokinetics study<sup>4</sup> involving 20 patients in palliative care using continuous subcutaneous fentanyl infusion of 100-5000mcg/day, there was a 8fold variation in total plasma concentrations and a 3.5 fold variation in unbound plasma concentrations. Hence there is considerable inter-patient variability in pharmacokinetics and careful titration according to individual clinical response is required.

### ***Oral transmucosal Fentanyl citrate (OTFC) in lozenge on a stick lollipop***

OTFC has been suggested to be used for incident pain. Its time to maximum concentration is 22 minutes and the onset of pain relief occurs at 5-10 minutes after application. The bioavailability is 0.52. It is under clinical trials for breakthrough pain. Whether it can be used for dyspneic spells needs further investigations. In addition, the use of sublingual fentanyl in liquid form as used in Patient 4 deserves further elucidation.

### ***Clinical Research for Subcutaneous Fentanyl infusion***

Intravenous and transdermal fentanyl has been used for a long time. The first study on the use of subcutaneous fentanyl was reported by Paix in 1995<sup>5</sup>. He retrospectively reviewed 11 patients given fentanyl because of significant adverse effects on opioids. All patients experienced an improvement in the adverse effect which prompted the change to fentanyl. Among the group, 5 patients presented with delirium, which resolved in all. The authors recommended the use of subcutaneous fentanyl infusion when subcutaneous or spinal morphine failed to abolish unacceptable opioid side effects.

In another retrospective review<sup>6</sup> of 22 hospice in-patients using subcutaneous fentanyl, the indications for its use were either unstable pain on transdermal fentanyl or opioid toxicity. The patients in pain on transdermal fentanyl had rapid control of pain after starting subcutaneous fentanyl. The conversion rate from transdermal to subcutaneous fentanyl was one to one.

Subcutaneous fentanyl and morphine were compared in a 6 days randomized, double-blind cross-over study of 23 stable hospice in-patients<sup>7</sup>. There were no significant differences in pain scores for the two groups; suggesting that fentanyl is as effective as morphine. The conversion ratio of morphine 10 mg to 150µg fentanyl was used. Patients in the fentanyl group from day 4-6 had more bowel motions. There were no significant differences in cognitive function and delirium in the two groups. This may have been due to patient selection, i.e. patients with morphine intolerance were excluded.

There is little information on the use of subcutaneous fentanyl in patient with renal failure. In a case report of a lady with intestinal obstruction and renal failure due to malignancy, subcutaneous fentanyl was used<sup>8</sup>. She had adequate pain control without sedation and confusion. The authors concluded that in the last days of life, morphine metabolites in patients with impaired renal function may cause opioid toxicity, including terminal agitation. As fentanyl has no active metabolites, it can be an alternative to morphine.

### ***Clinical study on sublingual Fentanyl citrate***

The effect of sublingual fentanyl citrate in the form of drops was evaluated in 11 hospice in-patients with cancer related breakthrough pain<sup>9</sup>. The sublingual dose given varied from 50 to 150µg for each pain episode. 55% of the patients had reduction of pain at 10 minutes, 85% at 15 minutes. Compared with usual breakthrough medication fentanyl was rated better(46%), the same(36%) or worse(18%). Advantages of sublingual fentanyl were the quick onset of action, no associated drowsiness and easy to use. No systemic adverse events occurred.

## Summary

From our experience of using fentanyl in the cases discussed and from the available clinical evidence, the use of fentanyl other than transdermal patch definitely worth exploration. Further research is in need to demonstrate its efficacy in the following situations when a trial of fentanyl may be justified:

1. Shift from transdermal fentanyl patch to subcutaneous route for easier titration, this avoids shifting to another opioid when subcutaneous administration is required;
2. A morphine substitute for patients with fear of morphine;
3. Rapid symptom control and dose titration because of fast onset and short half-life;
4. Easier prescription in renal failure because of the absence of active metabolites and independence of renal excretion; thus avoids the need for regular renal function assessment;
5. As another option of alternative opioid; and
6. The role of sublingual route in controlling breakthrough pain & dyspnoea.

<sup>1</sup> Osborne RJ, et al. Morphine intoxication in renal failure: the role of morphine-6-glucuronides. *BMJ* 1986; 292: 1548-1549.

<sup>2</sup> Haberer JP, et al. Fentanyl pharmacokinetics in anesthetized patients with cirrhosis. *Br J Anaesth* 1982; 54:1267-70.

<sup>3</sup> Moore RA, et al. Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; 1:829-58.

<sup>4</sup> Miller RS, et al. Plasma concentrations of Fentanyl with subcutaneous infusion in palliative care patients. *Br J Clin Pharmacology* 1995; 40(6): 553-6.

<sup>5</sup> Paix A, Coleman A, Lees J, Grigson J, Brooksbank M, Thorne D, Ashby M. Subcutaneous fentanyl and sufentanil infusion substitution for morphine intolerance in cancer pain management. *Pain*, 1995; 63:263-69.

<sup>6</sup> Watanabe S, Pereira J, Hanson J, Bruera E. Fentanyl by continuous subcutaneous infusion for the management of cancer pain: A retrospective study. *J Pain Symptom Manage*, 1998; 16:323-26.

<sup>7</sup> Hunt R, Fazekas B, Thorne D, Brooksbank M. A comparison of subcutaneous morphine and fentanyl in hospice cancer patients. *J Pain Symptom Manage*, 1999; 18:111-19.

<sup>8</sup> Mercadante S, Caligara M, Sapio M, Serretta R, Lodi F. Subcutaneous fentanyl infusion in a patient with bowel obstruction and renal failure. *J Pain Symptom Manage*, 1997; 13:241-44.

<sup>9</sup> Zeppetella G. Sublingual fentanyl citrate for cancer-related breakthrough pain: a pilot study. *J Pain Symptom Manage*, 2001; 15:323-28.