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## Safety of Chronic Transdermal Fentanyl Use in Patients on Hemodialysis

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### Keywords

fentanyl; transdermal; patch; end stage renal disease; hemodialysis; pain; opioid; sickle cell disease

Patients with end stage renal disease (ESRD) on renal replacement therapy frequently experience multifactorial chronic pain. Pain management in ESRD patients can be challenging because certain opioids, such as codeine and morphine, have active metabolites which are excreted through the kidney and accumulate in patients with renal impairment<sup>1</sup>. Limited evidence supports the intravenous (IV) or subcutaneous (SC) routes of fentanyl for short-term use in ESRD patients requiring hemodialysis (HD)<sup>2, 3</sup>. However, the safety of using a transdermal fentanyl patch for chronic pain management in ESRD patients is lacking. In this report, two ESRD patients with sickle cell disease (SCD) were safely treated with transdermal fentanyl for chronic pain while receiving HD.

1. A 40 year-old female with SCD and ESRD on HD was hospitalized for a vaso-occlusive pain crisis (VOC) which was uncontrolled by methadone 20 mg PO Q8H and hydromorphone 1 mg IV Q2H PRN for pain. Methadone was discontinued on day 13 of hospitalization after the patient experienced myoclonus. Subsequently, a transdermal fentanyl patch 50 mcg/hr was added to the IV hydromorphone regimen and the pain score improved from 8–10/10 to 6–8/10 within three days of therapy. The oxygen saturation remained above 96% on room air and the patient was awake and alert with a sedation score = 1. The patient was discharged home with a fentanyl patch 75 mcg/hr along with hydromorphone 4mg PO Q4H PRN for pain. In the next three years, the dose of the transdermal fentanyl patch was gradually increased to 500 mcg/hr without significant side effects while the patient continued HD.
2. A 28 year-old male with SCD and ESRD on HD was admitted to the hospital to manage a VOC episode. This patient previously had prolonged QTc intervals while taking methadone. On day 1 of hospitalization, a transdermal fentanyl

patch 50 mcg/hr along with IV hydromorphone patient-controlled analgesia (PCA) was started. His pain score improved from 8/10 to 6/10 with his oxygen saturation remaining above 97% on room air and the patient was awake and alert with a sedation score 1. The patient was discharged on a transdermal fentanyl patch 50 mcg/hr with hydromorphone 4 mg PO Q4H PRN for pain. The patient tolerated the pain regimen well at home and the fentanyl patch dose was increased to 100 mcg/hr in a subsequent hospitalization one month later. The patient continued the fentanyl patch for three months while receiving HD.

The most commonly prescribed long-acting opioids for chronic pain in the general population include morphine, oxycodone, methadone, and the transdermal fentanyl patch. The accumulation of active morphine metabolites in patients with renal dysfunction leads to a higher risk of adverse events in ESRD<sup>1</sup>. Oxycodone and its metabolites exhibit delayed elimination in renal impairment and there is evidence for toxicity associated with oxycodone use in renal failure<sup>4</sup>. The dosing of methadone is complicated. It has a long half-life, is highly protein-bound, and has potential side effects such as prolonged QTc intervals that raise the risk of dangerous cardiac arrhythmias. Fentanyl is a highly potent synthetic opioid with a short half-life. It undergoes rapid biotransformation in the liver and is converted to biologically inactive metabolites, including norfentanyl<sup>5</sup>. The parent drug and metabolites are eliminated predominantly through the kidney. Due to its high molecular weight, large volume of distribution, and protein binding, fentanyl is not expected to be dialyzable<sup>6</sup>. However, fentanyl could be removed by certain HD filters by absorbing onto the dialyzer membrane<sup>6</sup>. The average clearance of fentanyl during kidney transplantation in patients with ESRD is lower and inter-individual variability is greater compared to patients without renal failure<sup>7</sup>. There are reports of successful short-term use of SC and IV fentanyl in patients with renal dysfunction<sup>2, 3</sup>. The pharmacokinetics of the transdermal fentanyl patch is different from IV or SC routes of administration. The transdermal route provides slower absorption and more sustained release of the active ingredient. Although the transdermal fentanyl patch is suited for managing chronic pain, the literature on its use in HD patients is lacking. The package insert recommends avoiding its use in patients with severe renal impairment due to the concern for reduced clearance in this patient population. One case series showed that a 25 mcg/hr transdermal fentanyl patch was safely used to treat pain in three patients on HD, although the treatment duration was unclear<sup>8</sup>. The two patient cases presented in this report suggest that the transdermal fentanyl patch can be used safely at high doses and for a long duration in SCD patients on HD.

In summary, we described two patients with SCD and ESRD on HD who were successfully treated with transdermal fentanyl patches for chronic pain without experiencing significant side effects. The treatment dose was high (100 and 500 mcg/hr), and the duration was three months and three years, respectively. Considering concerns about the safety of other long-acting opioids in ESRD patients, the fentanyl patch may be a safe option in individuals on HD while requiring long acting opioids for pain control.

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