CASE REPORT

Not so patchy story of attempted suicide...leading to 24 hours of deep sleep and survival!

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SUMMARY

Here, we present a somewhat unusual suicide attempt where, despite an unbelievable overdose with transdermal fentanyl patches, the patient survived. The patient—a woman aged 70 years, who has suffered from chronic back pain despite starting transdermal fentanyl patches in 2007. The unconventional method of attempted suicide was based on online research into deaths from fentanyl patch toxicity. She had gradually accumulated 100 µg fentanyl patches from repeat prescriptions, applying 14 patches with fatal intent, alongside 2 45 mg mirtazapine tablets, and concurrent therapeutic doses of tramadol and morphine sulfate oral solution. However, after 24 hours, she awoke from a deep sleep to the sound of the telephone ringing, somewhat amazed her drastic efforts had failed. During admission to Great Western hospital, she was seen by liaison psychiatry and subsequently transferred to the care of the pain management team, to which she had already been referred.

A reminder of the normal pharmacokinetic profile of transdermal fentanyl.⁶

- ▶ **Absorption**—Transdermal patches provide continuous systemic delivery of fentanyl over the 72 hour administration period. In '100' µg patches, 100 µg is released each hour for 72 hours. The concentration gradient existing between the matrix and the lower concentration in the skin drives drug release.
- ▶ **Distribution**—The plasma–protein binding of fentanyl is ~84%.
- ▶ **Metabolism**—Fentanyl is a high clearance drug, rapidly and extensively metabolised primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, is inactive. Skin does not appear to metabolise fentanyl delivered transdermally.
- ▶ **Elimination**—After the patch is removed, serum fentanyl concentrations decline gradually, falling about 50% in about 17 (range 13–22) hours following a 24-hour application.

BACKGROUND

Chronic back pain is a common condition and understandably a cause of psychological distress. Meta-analysis has highlighted that individuals with physical pain conditions are more likely to report a lifetime suicide attempt.¹ We are reminded of two ways in which treatment for pain itself can also feed into this complex relationship, with higher prescribed opioid doses associated with increased risk of suicide,² and the potential for the paradoxical phenomenon of opioid-induced hyperalgesia.³

An American paper found that of 908 patients receiving long-term opioid therapy for pain, 37.7% reported suicidal ideation, and 20.5% reported suicidal attempt at some point during their lives.⁴ Among adults over 60 years of age, another study has highlighted an increasing linear trend for suicidal intent and mortality with opioid use between 2006 and 2013.⁵

With an ageing population, we can anticipate an increased burden of chronic disease and inevitable interplay between pain, treatment and psychological distress. This raises the question of whether better knowledge and training of GPs and more specialist pain services are needed in the community, especially with regard to understanding opioid dosing of fentanyl patches. Indeed, in retrospect, this patient had a rapid escalation of fentanyl from 25 to 100 µg over 7 weeks in 2007, which may well have been an early indication for the complexity of her pain management.

This case importantly highlights several key features

1. We found no other reported cases of individuals surviving such lethal transdermal opioid dosage over 24 hours without medical intervention—how was this patient able to survive?
2. Despite a high dose of opioid therapy, this patient had chronic pain, suggesting that they were ineffective for her.
3. Chronic pain has a strong association with psychological distress.
4. How can the healthcare system become more vigilant in preventing future cases of attempted suicide?

CASE PRESENTATION**Key points from the medical history**

The patient suffers chronic non-malignant back pain from severe lumbar scoliosis, and osteoarthritis in several joints. Therapeutic interventions have included spinal decompression surgery in 2012, and joint injections before this in 2011. In 2009, she was diagnosed with breast cancer and treated with surgery and chemotherapy which was stopped prematurely due to the side effects experienced. The patient was diagnosed with a generalised anxiety disorder in 2008, but had not been prescribed serotonin reuptake inhibitors.

Over the 2 months leading to her suicide attempt, the patient was started on daily mirtazapine 15 mg. It is not unreasonable to conclude that her chronic pain and cancer diagnosis may have

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been contributing factors to psychological distress and an eventual suicide attempt.

Overview of analgesic history

Opioid analgesics were first prescribed in November 2006, with transdermal buprenorphine increased from 5 to 20 µg by April 2007. This was changed to fentanyl patches in October 2007, rapidly increased from 25 to 100 µg over a period of 7 weeks. However, in the light of drowsiness and nausea, this was subsequently converted to modified-release oxycodone 10 mg twice a day and the patient was referred to orthopaedics regarding her lumbar scoliosis. The patient did not attend the appointments with orthopaedic surgeon or physiotherapist and restarted fentanyl 100 µg patches.

After a diagnosis of breast cancer in May 2009 and treatment with wide local excision, sentinel node biopsy, re-excision and chemotherapy, the patient was also prescribed morphine sulfate solution (Oramorph) and had two more prescriptions over several months. Chronic back pain still persisted and in December 2010, she was prescribed an extra 50 µg fentanyl to take in addition to her 100 µg fentanyl patch and Oramorph.

She had facet joint injections in 2011 and spinal decompression surgery in 2012. During this period, she was on a repeat prescription for Oramorph as well as a repeat prescription of 20 100 µg fentanyl patches every 2 months.

In 2014, a different GP at the practice became concerned that the frequency of Oramorph requests indicated each 300 mL bottle was lasting only 3 days. These concerns were discussed with the patient in mid-July and it was agreed to review medications following a pain clinic appointment, scheduled for the following month. In the meantime, the patient was advised to take no more than 20 mL of Oramorph per day in the light of her daily 100 µg fentanyl patch.

However, in July 2014, the patient presented to the emergency department after an intentional overdose with 14 100 µg transdermal fentanyl patches.

INVESTIGATIONS

In the emergency department, blood tests found urea and electrolytes, liver function tests and clotting to be within normal ranges.

Paracetamol levels were also checked and found to be zero.

OUTCOME AND FOLLOW-UP

The patient was admitted to Great Western Hospital and reviewed by the liaison Psychiatry team in accordance with Trust policy for all presentations of deliberate self-poisoning. She was discharged after being deemed no longer at risk, and seen by Avon and Wiltshire Intensive services twice more at follow-up appointments after the suicide attempt, before being discharged from this service. She has since had access to community psychiatric nurse services via her GP, but her care is primarily managed by a multidisciplinary pain team, including the psychology services available to all patients using the pain services. She continues to use a lower dose of fentanyl patches, and takes duloxetine to help with mood. In her latest appointment with the pain psychology services, she described feeling better emotionally with an improved quality of life.

DISCUSSION

We found no evidence that this patient had insensitivity to opioids outside of her extensive pain history that might help explain her survival. Moreover, we found no other cases that

have survived deliberate self-poisoning with such a high dose of transdermal fentanyl.

However, a literature search highlighted three other case reports of suicide by fentanyl patches in adults; in a woman aged 42 years with 11 100 µg patches,⁷ an assisted suicide of a woman aged 46 years with 34 mixed dose patches,⁸ and suicide of a woman aged 78 years with 10 100 µg patches.⁹ These cases are a testament to the lethality of fentanyl dose presented here, and how remarkable it was that the patient was able to survive.

Regarding age-related changes in pharmacokinetics, electronic medicines compendium recommends careful observation for signs of fentanyl toxicity in the elderly, due to data suggesting a prolonged half-life and increased sensitivity to fentanyl.⁶ However, results from a study using transdermal fentanyl are also mentioned, where fentanyl pharmacokinetics in elderly patients did not differ significantly from young patients, although peak serum concentrations tended to be lower and the mean half-life values were prolonged to ~34 hours.⁶

A crucial aspect of the pharmacokinetic profile is the dependency on a high matrix:skin concentration gradient for systemic fentanyl absorption. Applying such a high dose of fentanyl to the skin would initially yield a high concentration gradient and subsequent rapid absorption. However, as the drug infiltrated the skin, the concentration gradient would dissipate, slowing the rate of absorption as equilibrium is reached sooner.

This patient had been gradually accumulating fentanyl patches from repeat 2 monthly batch prescriptions, raising one possible explanation that the patches had reached their expiry date with a deteriorated matrix delivery system, below the expected 100 µg/hour/patch rate of absorption. Although a hypothetical claim, online searches reveal forums where patients misusing opioids are asking similar questions about potency and expiry dates, hence is worth considering when informing patients about fentanyl patch prescription.

A recent review has demonstrated that gene polymorphisms of the cytochrome P450 enzyme such as 'CYP3A5×3', can increase or decrease metabolism and hence subsequent elimination of fentanyl. Perhaps it is feasible that this patient had a polymorphism of this common enzymatic system, favouring a rapid metabolism of active fentanyl to inactive norfentanyl metabolites.¹⁰

Wider implications

Opioids Aware is part of a Public Health England funded project offering advice to healthcare professionals on opioid prescribing. The following pieces of advice are taken from their website,¹¹ and have particular relevance to this case:

1. There is little evidence for opioid effectiveness in long-term pain relief.
2. A small proportion of people may benefit from opioid use longer term if the dose can be kept low and if their use is intermittent; however, it is difficult to identify these people at point of initiation.
3. The risk of harm substantially increases at doses above the morphine equivalent of 120 mg/day, with no increased benefit. One fentanyl 100 µg patch is equivalent to ~360 mg/day of oral morphine.
4. If a patient remains in pain on opioids, they are not effective and should be discontinued even if no other treatment is available.
5. Chronic pain is complex and if patients have refractory, disabling symptoms, a detailed assessment of the many emotional influences on their pain experience is essential.

Learning points

- ▶ Clinically speaking, this patient should not have survived such a lethal dose. Her good fortune provides us as clinicians a rare opportunity to learn from this case to help prevent cases like these from happening again.
- ▶ Owing to the complex interplay between chronic pain, opioid use and psychological distress, we should regularly assess a patient's mental well-being and understanding of opioid lethality.
- ▶ Should pain management clinics be offered in primary care, so that expert advice can be made more accessible to patients?
- ▶ While the prescribing of opiate analgesics in UK is controlled, the online market, including the level of advice offered to customers, is considerably less so.
- ▶ When prescribing opiate analgesia to patients who have a background of mental illness, caution and the distinct possibility of suicidal intent should be explored early on.

Contributors AJT (medical student), HS (medical student) and LW (Associate Specialist, Pain team Great Western Hospital) have made substantial contributions to the conception of this case report, including acquisition and writing of the patient's medical history, and formulating a discussion including literature that relates to the case presented here. All authors have helped to plan and draft the work and revised it critically for important intellectual content, and have given approval of this final version to be published. All authors are in agreement to be accountable for all aspects of the work in ensuring any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LW is responsible

for acquisition of patient medical history. AJT contributed to regarding chronic pain, opioids and suicide attempts, previous related case reports and wider implications. HS contributed to regarding pharmacokinetics of fentanyl, age-related changes and potential for polymorphism-induced insensitivity.

Competing interests None declared.

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