Opioid-induced adrenal insufficiency in transdermal fentanyl treatment: a revisited diagnosis in clinical setting

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Abstract. Opioids are widely used for treatment of acute and chronic pain. However, opioids have several well-known clinical adverse effects such as constipation, nausea, respiratory depression and drowsiness [ 1]. Endocrine dysfunctions in hypothalamus and pituitary such as hypogonadotropic hypogonadism are also opioid-induced adverse effects [2-9]. Nevertheless, opioid-induced adrenal insufficiency (OIAI) has been rarely explored in patients with chronic pain. OIAI can be difficult to diagnose because the symptoms are usually non-specific and easily confounded with underlying conditions or opioid-related adverse effects [10, 11]. On the other hand, in actual clinical settings it may be recognized as only a very rare endocrinopathy due to its abundant documentation in preclinical studies and subjects with drug abuse [12-15]. Only one case of OIAI, in which morphine and transdermal fentanyl were both used, has been reported in Japan [16]; the apparent rarity might also be a hinderance to physician awareness of the clinical possibility of OIAI.

Fentanyl is one of the oldest synthetic piperidine opioid agonists, interacting primarily with mu (μ) receptors. It is approximately 80 times more potent than morphine [17]. The low-molecular weight, high potency and lipid solubility of fentanyl make it suitable for delivery by transdermal therapeutic system [18]. In addition, compared with oral opioids, transdermal fentanyl is less likely to induce adverse effects such as constipation, nausea and vomiting or daytime sleepiness [19].
Transdermal fentanyl was approved for clinical use in 2002 worldwide including Japan. While the frequency and dose of clinical opioids including fentanyl in Asian countries have remained both less and smaller, respectively, than those in Western countries [20], clinical opioid use has recently become much more widespread in Asia [20]. Moreover, the clinical application of transdermal fentanyl was expanded in Japan to non-malignant pain in 2010. Thus, more common use of opioids, especially transdermal fentanyl, is expected; at the same time, more careful attention to opioid-induced endocrinopathies including adrenal insufficiency is warranted.

We report a case of OIAI associated with use of transdermal fentanyl for non-malignant chronic pain. This is the first reported Japanese case of OIAI due to transdermal fentanyl alone. The present case highlights the importance of clinical vigilance for OIAI in patients with chronic opioid use and recommends further clinical contributions of endocrinologists in problematic opioid treatment cases.

**Case Presentation**

A 46-year-old female was referred to our department for evaluation and treatment of adrenal insufficiency. She had a history of dyslipidemia and migraine. She had not received any previous glucocorticoid treatment and she denied drug addiction. She gave birth at 24 years of age, with normal delivery and no massive bleeding. She had no family history of adrenal insufficiency or pituitary dysfunctions.

Her medical history revealed that at 41 years of age she received a total hysterectomy for uterine fibroids and, after the surgery, developed right buttock rhabdomyolysis. Subsequently, she suffered from pain in the right buttck and dorsal side of the left thigh. The pain was thought to be neuropathic pain and medications such as pregabalin and tramadol hydrochloride acetaminophen were initiated but were not effective. Therefore, seven months after onset of the pain, transdermal fentanyl was administered, and she was referred to the pain clinic department in our hospital for further treatment. As transdermal fentanyl reduced her pain, the treatment was continued. As an alternative, meixeltine and ketamine were tried but discontinued due to nausea. Clonazepam and lumbar sympathetic block were then added but did not permit reduction or discontinuation of transdermal fentanyl. Consequently, she continued to receive a relatively high dose of transdermal fentanyl [90–120 mg daily morphine milligram equivalent (MME)]. During treatment for the chronic pain, fatigue and loss of appetite, a decrease in vitality ensued and became worse about two years after starting fentanyl and was diagnosed as depression by a psychiatrist. Subsequently, nausea and constipation appeared, which are also considered common adverse effects of fentanyl. Antiemetics and stool softeners were initiated for nausea and constipation, respectively.

At 46 years of age, about four years after starting opioids, her defecation disorder became worse. Although naldeemedine was initiated, little improvement was seen. One month before the referral to our department, she was admitted to the general medicine department in another hospital for abdominal pain and constipation. For the purpose of understanding the constipation, an endocrine examination in early morning was performed. Laboratory data revealed decreased levels of plasma adrenocorticotropic hormone (ACTH) and cortisol (5.0 pg/mL and 1.9 μg/dL, respectively). After starting to take hydrocortisone 10 mg per day on the clinical suspicion of secondary adrenal insufficiency, she was referred to our department and admitted for further evaluation.

On admission, she was alert; height, 157.9 cm; weight, 48 kg (body mass index: 19.2 kg/m²); pulse, 80 beats per minute; blood pressure, 115/75 mmHg; and body temperature, 36.3°C. No self-injection scars were observed. She was prescribed transdermal fentanyl [3.0–3.5 mg semel in die (s.i.d)], clonazepam [2.0 mg ter in die (t.i.d)], zolpidem (5.0 mg s.i.d), mosapride (15 mg t.i.d), naldeemedine (0.2 mg s.i.d), herbal medicine keishikashakuyakudaimaoto (7.5 mg t.i.d), herbal medicine daiken-chuto (7.5 mg t.i.d), and hydrocortisone (10 mg bis in die).

Laboratory data is shown in Table 1. Endocrine data at fasting in early morning revealed decreased levels of plasma ACTH and cortisol (4.7 pg/mL and 2.1 μg/dL, respectively). Serum dehydroepiandrosterone-sulfate was also low (39 μg/dL, normal range 41–218 μg/dL). Corticotropin-releasing hormone (CRH)-stimulated ACTH response was overreaction, and cortisol response was blunted (Table 2). In rapid ACTH stimulation test, cortisol response was still slightly blunted (a baseline level of 1.9 μg/dL to a peak level of 15.0 μg/dL at 60 minutes after stimulation). Growth hormone-releasing peptide 2-stimulated ACTH response was overreaction, and cortisol response was blunted whereas growth hormone response was normal (Table 3). These profiles were consistent with secondary adrenal insufficiency, although repeating ACTH stimulation test and/or insulin tolerance test was not performed due to her refusal and our concerns for psychological burden. Luteinizing hormone releasing hormone-stimulated luteinizing hormone response was normal but follicle stimulating hormone response was delayed (Table 2). Thyrotropin-releasing hormone-stimulated thyroid stimulating hormone and prolactin responses were normal (Table 2). Enhanced
magnetic resonance imaging showed no abnormal findings of the hypothalamus and pituitary gland. Thus, the cause of secondary adrenal insufficiency in the present case was considered to be long-term use of transdermal fentanyl. Although elimination or reduction of fentanyl was attempted for possible recovery of the hypothalamic-pituitary-adrenal (HPA) axis, opioid-rotation and dose-reduction of transdermal fentanyl could not be performed because of the patient’s persistent pain and severe anxiety. On the other hand, continuation of oral corticosteroid replacement (15 mg per day) reestablished abdominal pain and constipation, while fatigue, appetite, and vitality were partially improved.

## Discussion

Here we report a rare case of OIAI. Our patient was treated with transdermal fentanyl for non-malignant chronic pain at a dose of 90–120 mg daily MME for four years; worsening constipation and abdominal pain led to suspicion of adrenal insufficiency. This is the first report of a Japanese case with OIAI due to transdermal fentanyl.

### Table 1  Laboratory data of the patient at fasting

| Parameter                  | Value         |
|----------------------------|---------------|
| White blood cell           | 3,660/μL      |
| Neutrophil                 | 47.5%         |
| Lymphocyte                 | 38.3%         |
| Monocyte                   | 10.1%         |
| Eosinophil                 | 3.3%          |
| Red blood cell             | 379 × 10^6/μL |
| Hemoglobin                 | 12.0 g/dL     |
| Hematocrit                 | 34.9%         |
| Platelet                   | 21.4 × 10^6/μL|
| Total protein              | 5.8 g/dL      |
| Albumin                    | 3.6 g/dL      |
| Total bilirubin            | 0.6 mg/dL     |
| AST                        | 15 IU/L       |
| ALT                        | 11 IU/L       |
| LDH                        | 131 IU/L      |
| γ-GTP                      | 18 IU/L       |
| Cholinesterase             | 238 IU/L      |
| ALP                        | 126 IU/L      |
| BUN                        | 8 mg/dL       |
| Creatinine                 | 0.55 mg/dL    |
| Uric acid                  | 3.0 mg/dL     |
| Na                         | 139 mEq/L     |
| K                          | 3.5 mEq/L     |
| Cl                         | 106 mEq/L     |
| Ca                         | 8.2 mg/dL     |
| P                          | 3.5 mg/dL     |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; HDL, high density lipoprotein; LDL, low density lipoprotein; FPG, fasting plasma glucose; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; PRL, prolactin; ACTH, adrenocorticotropic hormone; DHEA-S, dehydroepiandrosterone sulfate; PRA, plasma renin activity; PAC, plasma aldosterone concentration.
alone. The clinical course highlights two important issues: long-term transdermal fentanyl treatment may contribute to the development of secondary adrenal insufficiency and the symptoms associated with OIAI are non-specific and complex, which can make its diagnosis difficult.

Clinical OIAI was originally documented in 1977 [21]; physiological effects of opioids on the HPA axis became known via preclinical studies and clinical studies in drug abuse subjects [12-14]. However, the disease has been rarely reported in patients with chronic pain; concerns that OIAI might be under-diagnosed in clinical settings have been raised, even though it is well-known that other endocrine systems can be affected by opioids (Table 4) [2, 22-25]. Recently, some reports have pointed to unrecognized OIAI in clinical settings in Western countries [6, 10, 25, 26]. One such study found that the prevalence of OIAI in patients taking chronic opioids was as high as 9% in a pain rehabilitation center [26]. In another study, secondary adrenal insufficiency was identified in 22.5% of opioid users based on ACTH or metyrapone stimulation test [25]. Additionally, in a systematic review and meta-analysis of the effects of opioids on endocrine systems, hypocortisolism was identified in 15% to 24% of opioid users [6]. However, a single center retrospective study found that only 7.5% of the patients with OIAI were correctly diagnosed [10], which indicates under-diagnosis of this clinical entity even in countries with wide clinical use of opioids.

The pathogenesis of OIAI is characterized mainly by suppression of CRH secretion in the hypothalamus as well as ACTH secretion in the pituitary gland [27]. In patients with non-malignant chronic pain who received intrathecal opioid infusion, mostly morphine, the 24-hour urinary free cortisol excretion and the cortisol response in insulin tolerance test was lower compared to that in patients without opioid use [2]. Although a possible direct effect on the adrenal glands is also suggested [5], laboratory findings of secondary adrenal insufficiency with the combination of long-term opioid use and exclusion of other hypothalamic-pituitary diseases strongly lead to clinical diagnosis of OIAI [26]. In the present case, the clinical diagnosis of OIAI was established based on the laboratory findings suggesting secondary adrenal insufficiency including CRH stimulation test, clinical history of long-term fentanyl use and exclusion of other hypothalamic-pituitary diseases such as tumors. The over-action of ACTH in CRH or growth hormone-releasing peptide 2 stimulation test suggested hypothalamic dysfunction, which is compatible with the pathophysiology of OIAI, although confirmatory evaluations including insulin tolerance test were not performed [28]. In addition, suppressed reaction of cortisol in ACTH stimulation test suggested sustained adrenal insufficiency, which was compatible with the patient’s persistent symptoms including abdominal pain and constipation; the repeating ACTH stimulation test was not feasible.

Transdermal fentanyl became clinically available in 2002; fentanyl itself was initially synthesized in 1960.

### Table 2  Results of CRH, LHRH, and TRH stimulation tests

| Time (min) | 0    | 15   | 30   | 60   | 90   | 120  |
|-----------|------|------|------|------|------|------|
| ACTH (pg/mL) | 4.7  | 97.1 | 92.9 | 79.8 | 67.6 | 46.8 |
| Cortisol (μg/dL) | 2.1  | 7.1  | 9.7  | 12.9 | 11.6 | 12.0 |
| LH (mIU/mL) | 6.5  | 50.6 | 45.8 | 44.5 | 45.8 |
| FSH (mIU/mL) | 4.1  | 5.8  | 6.3  | 6.5  | 6.7  |
| TSH (μU/mL) | 2.26 | 37.95| 22.56| 17.77| 12.94|
| PRL (ng/mL) | 8.8  | 186.6| 88.9 | 60.5 | 40.2 |

CRH, corticotropin-releasing hormone; LHRH, luteinizing hormone releasing hormone; TRH, thyrotropin-releasing hormone; ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; PRL, prolactin.

### Table 3  Result of Growth hormone-releasing peptide 2 stimulation test

| Time (min) | 0    | 15   | 30   | 45   | 60   |
|------------|------|------|------|------|------|
| ACTH (pg/mL) | 6.9  | 39.7 | 29.1 | 21.4 | 15.1 |
| Cortisol (μg/dL) | 1.5  | 4.6  | 6.4  | 6.3  | 5.4  |
| GH (ng/mL) | 0.5  | 22.36| 79.69| 67.48| 40.76|

ACTH, adrenocorticotropic hormone; GH, growth hormone.
The first case of adrenal insufficiency due to transdermal fentanyl was described in 2005 [29]. There is little knowledge of adrenal insufficiency due to transdermal fentanyl use compared to that of other opioid agents such as morphine (Table 5) [2, 23, 25, 26, 29, 30], partly because it is a relatively new formulation with unique pharmacodynamics [18]. In Japan, transdermal fentanyl was approved for cancer-related pain in 2002 and its clinical application was expanded to non-cancer chronic pain in 2010. Although clinical use of opioids including transdermal fentanyl has become common in Japan, only one report regarding a Japanese case with OIAI could be found, which was due to the combination of transdermal fentanyl and morphine and was published in Japanese

### Table 4 Summary of opioid-associated hypothalamic-pituitary-end organ axes except for hypothalamic-pituitary-adrenal axis

| Affected axis                        | Evaluation method                             | First author, Year |
|--------------------------------------|-----------------------------------------------|--------------------|
| Hypothalamic-pituitary-gonadal axis  | Serum total or free testosterone: low         | Wong, 2011 [22],   |
|                                      | Gonadotropin-releasing hormone stimulation    |                   |
|                                      | test: low peak LH and FSH                    | Valverde-Filho,    |
|                                      |                                               | 2015 [23]          |
| Hypothalamic-pituitary-thyroid axis  | Serum FT4: low                               | Lamprecht, 2018    |
|                                      | Thyrotropin-releasing hormone stimulation     | [25]               |
|                                      | test: low peak TSH                            | Valverde-Filho,    |
|                                      |                                               | 2015 [23]          |
| Hypothalamic-pituitary-somatotropic  | Serum IGF-1: low                             | Abs, 2000 [2],     |
| axis                                 |                                              | Lampechte, 2018    |
|                                      | insulin tolerance test: low peak GH           | 2018 [25]          |
| Prolactin                            | Serum prolactin levels: high                 | Rhodin, 2010 [24],|
|                                      |                                               | Wong, 2011 [22]    |
|                                      |                                               |                    |

LH, luteinizing hormone; FSH, follicle stimulating hormone; FT4, free thyroxine; TSH, thyroid stimulating hormone; IGF-1, insulin-like growth factor 1; GH, growth hormone.

### Table 5 Summary of previous reports on opioid-induced adrenal insufficiency for each type of opioid

| Opioid type | First author, Year | No. of patients | Route of administration | Daily MME (mg) | Duration of opioid therapy (month) | Evaluation method of HPA axis | Affected other axes |
|-------------|---------------------|-----------------|-------------------------|----------------|------------------------------------|------------------------------|---------------------|
| Fentanyl    | The present case    | 1               | Transdermal             | 90–120         | 48                                 | Morning cortisol, 24-hour    | Possibly HPG axis   |
|             |                     |                 |                         |                |                                    | urinary free cortisol: low   |                     |
|             |                     |                 |                         |                |                                    | CRH stimulation test:        |                     |
|             |                     |                 |                         |                |                                    | overreaction to ACTH and     |                     |
|             |                     |                 |                         |                |                                    | blunt response to cortisol   |                     |
|             | Oltmanns, 2005 [29]| 1               | Transdermal             | 480            | 24                                 | CRH stimulation test:        | N/D                 |
|             |                     |                 |                         |                |                                    | blunt response to ACTH and    |                     |
|             |                     |                 |                         |                |                                    | cortisol                      |                     |
|             |                     |                 |                         |                |                                    | HPA axis                      |                     |
|             | Abs, 2000 [2]       | 73              | Intra-thecal            | Mean 1,440 ± 960 SD | Mean 26.6 ± 16.3 SD | 24-hour urinary free cortisol: | HPG axis            |
|             |                     |                 | (hydromorphone, n = 5)  |                |                                    | low (19.7%)                   |                     |
|             |                     |                 |                         |                |                                    | ITT: low peak cortisol (14.8%)|                     |
|             | Valverde-Filho, 2015 [23]| 38     | Intra-thecal           | Median 1,050 (IQR, 450–1,500) | Median 24 (IQR, 12–90) | Morning cortisol: low (Intra-thecal 33.3%, Oral 22.2%) | HPG axis            |
|             |                     |                 |                         |                |                                    | ITT: low peak cortisol        | HPS axis            |
|             |                     |                 |                         |                |                                    | (Intra-thecal 33.3%, Oral 50%)| HPT axis            |
|             | Oral                | Median 30 (IQR, 30–40) | Median 12 (IQR, 8–19) |    |                                    |                              |                     |
| Oxycodone   | Lampechte, 2018 [25]| 40              | Oral, Transdermal      | Mean 74 (range, 25–265) | Mean 48 (range, 12–300) | Morning cortisol: low (20%) | HPG axis            |
|             |                     |                 | (mostly oxycodone)     |                |                                    | ACTH or metyrapone stimulation test: blunt response to cortisol (22.5%)|                     |
|             | Li, 2020 [26]       | 102             | N/D (mostly oxycodone) | Median 60 (range, 3–840) | Median 60 (range, 3–360) | Morning cortisol, ACTH, and DHEA-S: low (9%) |                     |
|             | Tramadol             | 1               | Oral                   | 15              | Up to 36                           | Synacthen test: low baseline cortisol and blunt response to cortisol | N/D                 |
|             | Debono, 2011 [30]   |                 |                        |                |                                    |                              |                     |

MME, morphine milligram equivalent; HPA, hypothalamic-pituitary-adrenal; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; HPG, hypothalamic-pituitary-gonadal; N/D, not date; SD, standard deviation; ITT, insulin tolerance test; HPS, hypothalamic-pituitary-somatotropic; IQR, interquartile range; HPT, hypothalamic-pituitary-thyroid; DHEA-S, dehydroepiandrosterone-sulfate.
In that case report, a 51-year-old man with chronic pain syndrome of his lower extremity was diagnosed as having hypogonadism and secondary adrenal insufficiency. He received transdermal fentanyl (60 mg daily MME) following four-year oral morphine treatment (50 mg per day). Fentanyl was then changed to tramadol and an oral corticosteroid replacement was given for OIAI. This case developed secondary adrenal insufficiency due to long-term opioid use, similarly to our present case. Our patient thus represents the first Japanese OIAI case induced by transdermal fentanyl alone.

The relatively high total dosage of fentanyl in the present case may have contributed to the development of adrenal insufficiency. Recent reports have pointed out that higher morphine-equivalent daily dose and longer duration of opioid use may be risk factors for adrenal insufficiency [10, 25, 26]. In a retrospective study, patients with OIAI, for whom the duration of opioid use was about 96 months, took higher daily MME dose of opioids than those without adrenal insufficiency [26]. In addition, no patients taking opioids at a dose less than 20 mg daily MME were diagnosed with OIAI. In another study, daily median and minimum MME doses in patients diagnosed with OIAI were 105 mg and 60 mg, respectively [10]. These findings are consistent with our case, in whom transdermal fentanyl usage was 90–120 mg daily MME for four years.

Another possible delay in affirmative diagnosis of OIAI should be noted. Partly because both adrenal insufficiency and opioid use can cause ambiguous symptoms, those of OIAI might be misunderstood as an effect of the primary disease, a common adverse effect of opioid use or a psychiatric disorder such as depression [10, 11, 31]. Thus, together with under-recognition of OIAI as a clinical possibility, the non-specific and wide-range of symptoms of OIAI can delay diagnosis, although delay can cause life-threatening events [31]. Indeed, Li T, et al. reported that median duration prior to diagnosis of OIAI was 12 months [10]. In the present case, abdominal pain, constipation, fatigue, appetite loss and vitality, which were recognized at least two years prior to the diagnosis of OIAI and initially thought to be effects of the primary disease or common adverse effects of opioids, were fully or partially ameliorated after oral corticosteroid replacement, suggesting that these symptoms were associated with adrenal insufficiency. Clinical vigilance for OIAI is therefore required for patients with long-term or high dosage opioids.

Finally, as treatment or prevention of OIAI, elimination, rotation, and reduction of opioid dose can be options for possible recovery of the HPA axis, along with corticosteroid replacement therapy [9]. In the present case, elimination or reduction of fentanyl could not be performed during the patient’s admission period due to her persistent pain and severe anxiety, but such treatment should be considered as future options.

In conclusion, we report a case of secondary adrenal insufficiency due to clinical transdermal fentanyl usage. Under-recognition of OIAI as a plausible clinical entity as well as its variety of symptoms can hamper prompt diagnosis. Vigilance for early signs of OIAI that enables effective corticosteroid replacement therapy is therefore essential for patients with long-term and/or high dose opioid usage.

Disclosure

None of the authors has potential conflicts of interest associated with this report.

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