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A Fentanyl Infusion Test to Guide Opioid Therapy in Complex Regional Pain Syndrome: A Case Report

Takuya Okada, MD, PhD, Kyohei Ueno, MD, Yuki Nomura, MD, PhD, Rina Miyazaki, MD, and Norihiko Obata, MD, PhD

Background: Complex regional pain syndrome (CRPS) is a chronic pain disorder characterized by disproportionate pain and autonomic disturbances, and its management remains challenging. Opioid therapy is controversial because analgesic responses vary considerably among patients.

Case Report: A 52-year-old woman developed CRPS type 1 after a crush injury to her right foot. She presented with severe persistent pain, allodynia, edema, and gait disturbance. A fentanyl infusion test (100 μg over 30 minutes) was performed to assess opioid responsiveness. Her Numeric Rating Scale score decreased from 8 to 3, indicating opioid-sensitive pain. Based on this response, tramadol therapy was initiated in combination with rehabilitation. The patient subsequently showed progressive pain relief and functional recovery, and tramadol was successfully tapered over 11 months.

Conclusions: Our case suggests that a fentanyl infusion test may help identify opioid-responsive patients with CRPS and guide individualized analgesic therapy while avoiding unnecessary opioid use.

Key words: Complex regional pain syndrome, fentanyl infusion test, opioid responsiveness, rehabilitation

BACKGROUND

Complex regional pain syndrome (CRPS) is a chronic pain disorder that typically develops after trauma or surgery and is characterized by disproportionate persistent pain, allodynia, edema, motor dysfunction, and skin color changes (1,2). Although relatively uncommon, CRPS can cause severe pain and disability, leading to profound restrictions in daily and social activities and a marked reduction in quality of life (3). Because of its diverse clinical presentation, both diagnosis and management remain challenging, and early appropriate intervention is critical for improving outcomes.

A wide range of treatment options have been proposed for the management of CRPS, including pharmacological therapies, rehabilitation, and nerve blocks; however, there is no established consensus regarding the optimal management (2,4). In particular, the efficacy of opioids varies considerably among patients, making it difficult to determine their appropriate usage. To address this issue, we employed a fentanyl infusion test, originally developed at our institution, as a rapid method to assess opioid sensitivity and guide therapeutic decision making. This approach enables a short-term evaluation of analgesic efficacy, thereby minimizing unnecessary opioid prescriptions while facilitating early initiation of therapy in suitable cases and further supporting individualized dose optimization through the prediction of adverse effects and simulation of plasma concentration.

Here, we present a case of CRPS in which opioid

From: Division of Anesthesiology, Department of Surgery Related, Kobe University, Graduate School of Medicine, Kobe, Hyogo, Japan

Corresponding Author: Takuya Okada, MD, PhD, E-mail: takuya_okada813@yahoo.co.jp
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responsiveness was confirmed using a fentanyl infusion test, enabling early initiation of pharmacological treatment and rehabilitation with a favorable clinical outcome. To our knowledge, our case illustrates how a short fentanyl infusion test may help assess opioid responsiveness and guide treatment decisions in CRPS. This test may provide a practical approach to assessing opioid responsiveness and guiding treatment decisions in patients with refractory pain, while also allowing estimation of potential adverse effects and dose optimization.

CASE PRESENTATION

A 52-year-old woman (height 166 cm, weight 50 kg) sustained a crush injury to the dorsum of her right foot, in October 2022, when it was run over by a car tire, resulting in a laceration and cuboid fracture. She received conservative treatment at a local orthopedic clinic; however, her pain persisted, and she was referred to our department 3 months later, in January 2023. The patient had no significant past medical history or comorbidities. At the time of referral, she was taking loxoprofen and neurotropin (a nonopioid analgesic derived from vaccinia virus-inoculated rabbit skin extract commonly used in Japan), but these were ineffective.

On initial examination, the patient reported severe continuous pain (Numeric Rating Scale [NRS-11] score of 8) extending from the dorsum of the right foot to the ankle, accompanied by allodynia, edema, and skin perfusion abnormalities, which resulted in gait disturbance and marked impairment in activities of daily living (Fig. 1A). No evidence of peripheral nerve injury was found, and she was diagnosed with CRPS type 1.

At our institution, the fentanyl infusion test is conducted with approval from the hospital's medical safety committee. Eligible patients were those with refractory pain and an NRS-11 score of ≥ 5, while patients at risk of opioid dependence or with psychiatric disorders were excluded. During the procedure, resuscitation equipment was prepared, and continuous monitoring of pulse oximetry and noninvasive blood pressure was performed.

A total dose of 100 μg fentanyl, diluted in 100 mL of saline, was infused intravenously over 30 minutes. The dose and infusion rate were determined based on pharmacokinetic simulations using the model by Shafer et al (5), which predict a peak plasma fentanyl concentration of approximately 1.7 ng/mL in a 50 kg adult. This concentration lies within the established analgesic range for fentanyl (0.5-2 ng/mL) while remaining below the threshold associated with respiratory depression (5). Plasma concentrations were simulated using the pharmacokinetic model by Shafer et al (5) implemented in STANPUMP software (Stanford University, Stanford, CA) without weight normalization. Although effect-site concentration may better reflect pharmacodynamic effects, plasma concentration was used in this protocol because it has been routinely applied in our institutional workflow. The 30-minute infusion allows for the gradual attainment of effective plasma levels, enabling real-time monitoring of the analgesic response and adverse effects. Pain intensity was evaluated using the NRS-11 before infusion, immediately after infusion, and at 15 and 30 minutes postinfusion. A reduction of ≥ 50% in the NRS-11 score is regarded as a positive response and is used to guide subsequent treatment decisions. The dose is reduced by half in elderly patients (≥ 80 years) or in those with malnutrition.

In this case, the NRS-11 score improved from 8 to 3 immediately after the infusion and remained at 3 at 30 minutes, indicating opioid-sensitive pain. Based on this response, oral tramadol hydrochloride 150 mg/d was initiated, combined with rehabilitation by a physical therapist. At the 2-week follow-up, the pain had markedly improved (Fig. 1B), and 2 weeks later, edema and skin perfusion abnormalities of the dorsum of the foot also resolved (Fig. 1C).

Tramadol was temporarily increased to 200 mg/d due to formulation changes but was subsequently tapered to 100 mg/d at 4 months, 75 mg/d at 6 months, and 50 mg/d at 11 months. Rehabilitation began with toe muscle training, followed by aquatic therapy, stretching and strengthening of the ankle and lower leg, and gait training. Motor function gradually improved, and by 11 months after the initial visit, the symptoms had almost completely resolved, with walking ability restored to a level comparable to that of a healthy individual (Fig. 2).

DISCUSSION

To our knowledge, reports describing a structured intravenous fentanyl infusion test used to guide opioid selection and dosing in CRPS are extremely limited, and standardized approaches for identifying opioid-responsive CRPS remain lacking. This approach may provide a practical method for rapidly identifying opioid-responsive patients and optimizing individualized treatment strategies.

CRPS commonly develops after trauma or surgery and is characterized by pain that is disproportionate to the

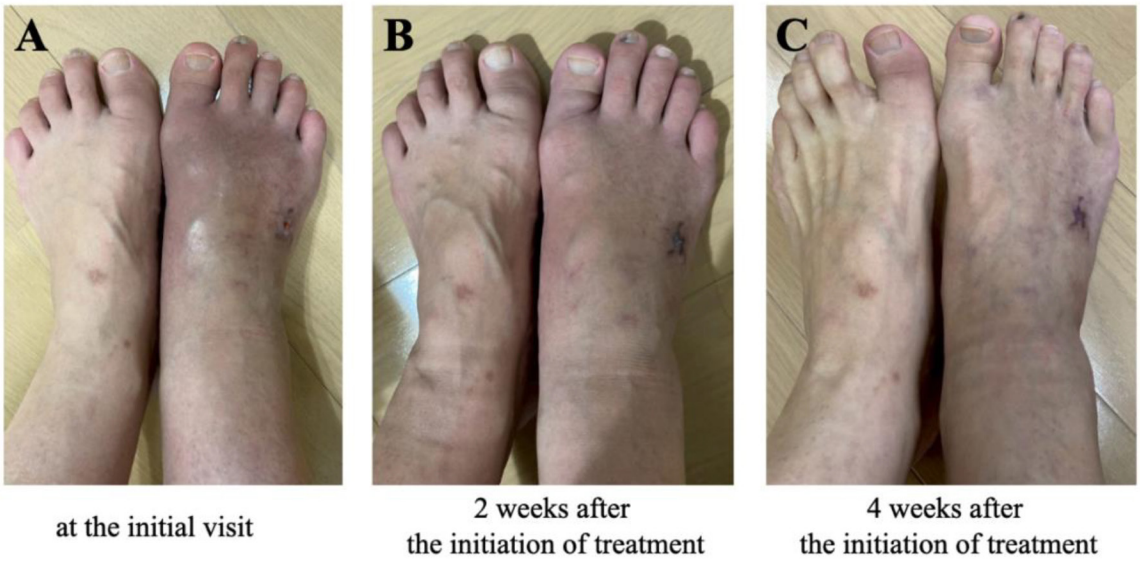


Fig. 1. Appearance of the right (affected) and left (unaffected) feet. (A) Initial visit showing edema and abnormal cutaneous blood flow in the right foot. (B) Two weeks after treatment. (C) Four weeks after treatment, edema and perfusion abnormalities markedly improved in the affected foot.

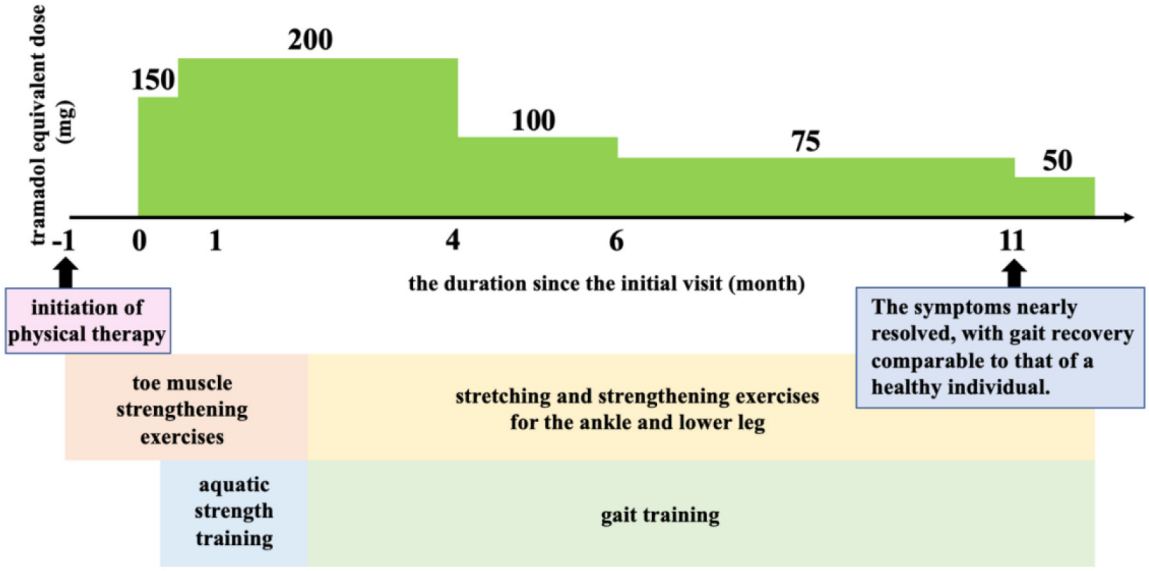


Fig. 2. Changes in tramadol dosage and physical therapy during the clinical course.

inciting event. Its clinical manifestations are diverse, including sensory disturbances (allodynia, hyperalgesia), vasomotor changes (skin color and temperature alterations), autonomic dysfunction, such as edema and abnormal sweating, and motor or trophic changes (weakness and atrophy) (1,2). The pathophysiology involves a complex interplay of peripheral and central sensitization, sympathetic dysfunction, and immune and inflammatory responses, but remains incompletely understood (6,7). Delayed diagnosis and treatment are associated with poor outcomes, highlighting the importance of early recognition and intervention (7,8).

The Budapest Criteria, revised by the International Association for the Study of Pain in 2010, are the current

international standard for diagnosis (9). They require disproportionate pain, symptoms in at least 3 of 4 categories, signs in at least 2 categories on examination, and exclusion of other diagnoses. Our patient met these criteria, presenting with persistent pain, marked allodynia, edema, vasomotor abnormalities, and activity limitation, and was diagnosed with CRPS type 1.

Treatment options for CRPS include pharmacological therapy (nonsteroidal anti-inflammatory drugs [NSAIDs], neuropathic pain agents, opioids, ketamine, bisphosphonates, and corticosteroids) and nonpharmacological approaches (rehabilitation, nerve blocks, spinal cord stimulation, cognitive behavioral therapy, and sympathectomy). However, the level of evidence for each treatment is limited, and management is often individualized (2,4). Early initiation of multimodal therapy has been reported to improve outcomes (7,8,10,11).

In our clinical practice, pharmacological treatment for CRPS is usually initiated with nonopioid agents, such as NSAIDs, neuropathic pain medications, and rehabilitation. The fentanyl infusion test is considered in selected patients when pain remains severe (NRS-11 $\geq$ 5) and interferes with participation in rehabilitation, in order to help determine whether opioid therapy may be beneficial.

Evidence supporting the efficacy of opioids in CRPS is scarce. Strong opioids must be used with caution owing to the risk of dependence, and guidelines recommend their use only selectively (12). The analgesic effect of opioids observed in our case may be attributable to multiple mechanisms, including: suppression of spinal dorsal horn neuronal hyperexcitability, leading to inhibition of central sensitization; attenuation of peripheral sensitization through reduced inflammatory cytokine release at nociceptive terminals; inhibition of sympathetic overactivity contributing to relief of sympathetically maintained pain; and activation of descending inhibitory pain pathways from the brainstem. However, the principal mechanism remains uncertain (6). Furthermore, in cases where severe pain prevents rehabilitation, appropriately selected opioid therapy has been reported to promote functional recovery (13). Tramadol, with dual μ-opioid receptor agonism and serotonin-norepinephrine reuptake inhibition, is considered a first-line opioid because of its relatively low dependence potential (12). In our patient, tramadol was tapered successfully without dependence, supporting its safety (Fig. 3).

Rehabilitation is the cornerstone of CRPS treatment. Early initiation, ideally within one year of onset, is associated with pain reduction and functional recovery (1,14). In our case, pain relief following tramadol therapy enabled progressive rehabilitation, resulting in marked improvement in the patient's activities of daily living (Fig. 3).

The fentanyl infusion test used at our institution involves intravenous administration of 100 μg fentanyl over 30 minutes with serial NRS-11 assessments. This simple procedure provides a rapid evaluation of opioid responsiveness, allowing unnecessary prescriptions to be avoided and facilitating early treatment in appropriate cases, while also supporting dose optimization through the prediction of adverse effects, such as nausea and respiratory depression, and simulation of plasma concentrations (Figs. 3 and 4) (5).

The protocol used in our institution is simple and reproducible because it requires only standard monitoring and a short infusion period, which may facilitate implementation in other pain clinics or perioperative settings.

Fentanyl was selected because an intravenous formulation of tramadol was not available at our institution. Compared with morphine, fentanyl has a faster onset of action, minimal renal and respiratory effects, and extensive clinical experience. In our case, the serotonergic and noradrenergic reuptake inhibition of tramadol may have contributed to its analgesic effects. Future studies using intravenous tramadol formulations are planned to refine the precision of opioid responsiveness tests.

Following fentanyl administration, the patient's NRS-11 score rapidly improved from 8 to 3, indicating high opioid sensitivity. Based on this response, tramadol therapy was initiated. As analgesia persisted even at a predicted plasma concentration of 0.47 ng/mL at 30 minutes after fentanyl infusion, the tramadol dose was determined as 150 mg/d. As shown in Fig. 3, tramadol 150 mg/d corresponds approximately to a fentanyl plasma concentration range of 0-0.5 ng/mL. Because analgesia was observed within this concentration range during the fentanyl infusion test, tramadol therapy was initiated at this dose. Effective pain relief subsequently facilitated rehabilitation, resulting in a marked improvement in the CRPS symptoms. The opioid conversion shown in Fig. 3 should be interpreted as an approximate clinical reference rather than a strict equianalgesic equivalence.

Our report does not advocate for opioid use in patients with CRPS but rather emphasizes the optimization of opioid therapy. At our institution, opioids are pre-

scribed with careful consideration of the risks of addiction and dependence and are used only as a temporary and effective treatment option. To avoid long-term use, a multimodal approach, including nerve blocks and spinal cord stimulation, is applied according to each patient's condition. Our case suggests that the fentanyl infusion test may help guide individualized opioid therapy in selected patients with CRPS, although further studies are required to confirm its reproducibility and clinical utility.

CONCLUSIONS

We reported a case of CRPS in which early initiation of appropriate pharmacological therapy and rehabilitation, guided by a fentanyl infusion test, resulted in a favorable outcome. Although CRPS is a refractory pain condition, some patients may respond to opioid analgesics. The fentanyl infusion test provides a practical means of evaluating opioid responsiveness, supporting individualized treatment decisions, and reducing unnecessary opioid prescriptions. This approach may also contribute to addressing the growing concerns regarding opioid dependence.

Fentanyl Plasma Concentration and Opioid Equianalgesic Conversion Table

Plasma fentanyl concentration	0～0.5 ng/mL	0.5～1.0 ng/mL	1.5～2.0 ng/mL
	↓	↓	↓
Transdermal fentanyl patch	1 mg	2 mg	4 mg
Oxycodone	20 mg	40 mg	80 mg
Tramadol	150 mg	300 mg	

Fig. 3. Plasma fentanyl concentrations were used to guide tramadol dosing and the opioid equivalence table.

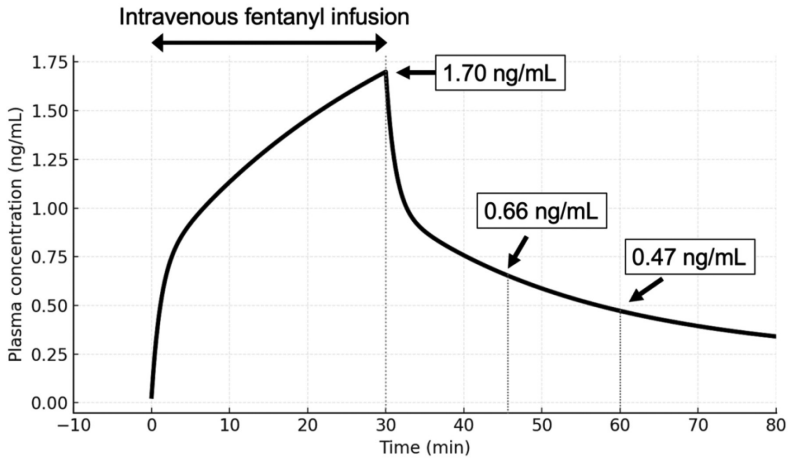


Fig. 4. Plasma fentanyl concentration profile during the test in this case. Plasma fentanyl concentrations were 1.7 ng/mL immediately after infusion, 0.66 ng/mL at 15 minutes, and 0.47 ng/mL at 30 minutes. The pharmacokinetic parameters were estimated using the model by Shafer et al (5).

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