



Unusual Route of Buprenorphine Administration: An Alternative Approach for Bypassing Adverse Drug Reactions

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ABSTRACT

Tramadol abuse is a critical and growing health concern in Asia. In Iran, tramadol abuse arises most commonly as a result of self-medicating that leads to tramadol dependence. Buprenorphine, a partial agonist of mu opioid receptors approved for the treatment of tramadol dependence, is administered sublingually due to its extensive first-pass metabolism and resulting low oral bioavailability. A 50-year-old man presenting with tramadol dependence after self-medicating for chronic low back pain experienced adverse reactions to a minimal dosage (0.8 mg) of sublingual buprenorphine. He was treated successfully with a modified protocol composed of swallowing sublingual tablets (0.2 mg/day initially, which increased to 0.2 mg every 12 hours during maintenance therapy). This unusual case suggests that swallowing buprenorphine sublingual tablets may prevent adverse effects and reduce the rate of treatment dropout.

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Introduction

Tramadol was approved in the United States in 1995 as an unscheduled centrally acting opioid analgesic¹ and introduced in Iran in 2002 for the relief of mild to moderate pain.² Although the mechanism of action is not fully understood, the analgesic effects of tramadol are mediated by 2 mechanisms: inhibition of serotonin and noradrenaline reuptake and binding of its metabolite (O-desmethyltramadol) to mu opioid receptors.³ Analgesia begins approximately 60 minutes after administration and peaks within 2 to 3 hours. Because Tramadol has mu-opioid agonist activity, the potential for its misuse and illegal use should be considered, especially in individuals with a history of substance abuse. Physician concerns about abuse and addiction in acute and chronic pain management should not prevent patients from receiving proper therapy.⁴

Use of opioid analgesics is associated with the risk of dependence even with correct management procedures, and therefore full assessment of patients for signs and symptoms of addiction

should be included in treatment protocols.⁵ Tramadol dependence may occur even after a few weeks of use at therapeutic doses,^{1,3} and is believed to arise due to its euphoric effects, including increased energy and improved mood, in addition to its analgesic effects.^{3,6,7} Opioid dependence is a serious problem worldwide, and health care providers have attempted to address this crucial situation through use of behavioral therapies and medications such as methadone and buprenorphine.⁸

In 2002, the Food and Drug Administration approved buprenorphine, a semisynthetic partial agonist of mu opioid receptors, for the treatment of opioid addiction; however, data on the treatment of tramadol dependence with buprenorphine are extremely limited.^{7,9} There are some benefits of buprenorphine over methadone in the treatment of opioid addiction, including less sedation, lower risk of toxicity at higher doses, and less withdrawal symptoms.⁹ Sublingual formulations of buprenorphine hydrochloride have been approved by the Food and Drug Administration for the treatment of opioid dependence.^{3,7,10} It has been reported that sublingual buprenorphine hydrochloride tablets have remarkable bioavailability (30%–50% of the intravenous route) and a prolonged half-life (28–37 hours), whereas buprenorphine bioavailability is dramatically reduced if swallowed (10% of the intravenous route) due to extensive first-pass metabolism and a short half-life (3 hours). It is not clear why there is such a large difference in half-life among

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different routes of buprenorphine administration⁹ and therefore, patients should be advised not to swallow buprenorphine sublingual tablets due to decreased effectiveness.^{9,10}

Case Presentation

A 50-year-old man with tramadol dependence sought treatment at our addiction center. His past medical history was significant for a 2-year period of opium addiction, which was resolved at age 44 years after he attended narcotics anonymous sessions. He had not taken any addictive substances thereafter. At the time he was referred to our addiction center, he had experienced chronic low back pain for 6 months due to disk bulging at L3 to L4 and L4 to L5 levels, as demonstrated by magnetic resonance imaging. Because his pain was resistant to treatment with common analgesics (ie, nonsteroidal anti-inflammatory drugs), he started self-medicating with tramadol at a dose of 50 mg daily, which led to relief of pain. Over 4 weeks, he increased the daily dose of tramadol to 200 mg due to experiencing both a return of pain and a craving to consume greater doses. When the patient forgot to consume tramadol or when he decreased the tramadol dosage, he experienced muscle stiffness, rhinorrhea, agitation, and headache. Because he had a history of drug dependence and was aware of its symptoms, he sought treatment for tramadol dependence. The patient underwent physical examinations and lab tests. He was not currently taking any prescribed medications or illicit drugs. His liver function tests, complete blood count, and urinary analysis were normal. Following the initial examination, he was diagnosed with substance use disorder according to the Diagnostic Statistical Manual-V criteria and buprenorphine maintenance therapy was initiated. He received a dose of 0.8 mg sublingual buprenorphine (2 buprenorphine 0.4 mg sublingual tablets, simultaneously). After 20 minutes, he experienced adverse effects of buprenorphine, including severe nausea and vomiting, dizziness, sedation, and miotic pupils. He was given metoclopramide IM, monitored for 3 hours, and discharged when his condition returned to normal. His buprenorphine dosage was decreased to 0.4 mg/d (as buprenorphine sublingual tablets). On the second and third days after this, despite receiving decreased doses of buprenorphine, he experienced similar adverse effects. Three days later, the patient returned to the addiction center and reported that he accidentally swallowed a half tablet of 0.4 mg buprenorphine (instead of sublingual consumption) without experiencing adverse effects. He continued this new dosing route (0.2 mg/d) as his buprenorphine initial treatment. Finally, after additional evaluations, the patient began buprenorphine maintenance therapy at a dosage of 0.2 mg every 12 hours, which was taken orally instead of by the sublingual route. The patient was successfully treated using this therapeutic regimen.

Discussion

Buprenorphine sublingual tablets, alone or in combination with naloxone, are indicated for treatment of opioid dependence. Tablets are administered sublingually at a dosing range of 12 to 16 mg/d, preferably when early signs of withdrawal appear.⁴ Buprenorphine plasma concentration peaks within 1 hour after sublingual administration. Some reported advantages of buprenorphine have included lower risk of toxicity at higher doses and better acceptance by patients and the public relative to methadone.⁸ Adverse reactions, including headache, sedation, dizziness, nausea and vomiting, and miosis occur in nearly 3% of patients.^{4,11,12} There are no adequate data on interindividual variations in the therapeutic dose, onset of action, adverse effects, tolerability, or any other unexpected events in real-world application.¹³

The patient presented here experienced almost all of the documented adverse reactions to buprenorphine despite having re-

ceived a dose several fold lower in magnitude than the approved therapeutic dose for the treatment of opioid dependence. In contrast to the information about buprenorphine pharmacokinetics reported in a drug reference handbook, these reactions were reported within a few minutes after sublingual administration. Although guidelines suggest that buprenorphine is safer relative to methadone due to a lower incidence of respiratory depression and lower mortality rate,⁸ these observations raise concerns about reduced tolerability and consequent patient dropout.

Swallowing buprenorphine sublingual tablet formulations may be a suitable strategy to prevent some of the most common adverse effects of buprenorphine when used to treat dependence, including nausea, dizziness, and sedation, and may help patients remain on treatment. As noted, only a small portion of a sublingual buprenorphine dose is absorbed by the oral mucosa, whereas a major portion is metabolized by first-pass metabolism in the liver,^{10,14} mainly by cytochrome P450 3A4 enzymes and clearance is proportional to hepatic blood flow.¹⁰ Thus, swallowing buprenorphine tablets could be used in patients who experience adverse effects to buprenorphine even after receiving very small doses. A possible explanation for this phenomenon could be that swallowing sublingual tablets decreases the absorption of buprenorphine via the oral mucosa and facilitates extensive first-pass metabolism, which leads to reduced bioavailability and lower plasma concentrations.^{14,15} Therefore, the oral route of administration may be particularly helpful for patients in whom very small doses of buprenorphine are effective and in whom avoidance of adverse effects is desirable.

Given the high prevalence of opioid abuse and safety of buprenorphine compared with methadone, it was postulated that swallowing buprenorphine tablets may be an alternative strategy to prevent buprenorphine adverse effects and increase the retention rate for buprenorphine maintenance therapy, particularly in patients who experience adverse effects. Further investigations should be conducted to evaluate this approach. To our knowledge, no previous report has indicated the effectiveness of such a low dose of buprenorphine.

Conclusions

In the case reported here, oral rather than sublingual buprenorphine was used successfully to treat tramadol dependence and manage low back pain. Swallowing very low dose sublingual buprenorphine tablets may be well tolerated and effective for both relief of pain and treatment of opioid dependence in patients who experience adverse effects such as nausea and vomiting, dizziness, sedation, and miotic pupils after sublingual buprenorphine.

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Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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