Interventional Pain Medicine 2 (2023) 100258

Contents lists available at ScienceDirect

Interventional Pain Medicine

journal homepage: www.journals.elsevier.com/interventional-pain-medicine

Sublingual buprenorphine-naloxone microdosing protocol to wean and explant intrathecal drug delivery systems for chronic non-cancer pain

1. Introduction

Chronic pain poses a large economic and health burden to our society as one of the most common reasons to seek medical care [1]. As many of these chronic pain conditions are refractory to conventional medical management, physicians have commonly used opioid medications for analgesia [1]. However, the role of opioids in chronic pain is questionable, especially given the potential for adverse effects, such as opioid-induced hyperalgesia at high doses, and opioid dependence after chronic use.

For patients with cancer and non-cancer chronic pain refractory to oral pharmacologic therapy, intrathecal drug delivery systems (IDDS) (also commonly called "pain pumps" or "pumps") are a relatively safe and effective interventional therapy. This is attributed to its high drug concentrations in the cerebrospinal fluid (CSF) but low concentrations in systemic circulation and therefore relatively decreased adverse effects [2]. Medications currently approved for IDDS by the United States Food and Drug Administration include morphine, ziconotide and baclofen, although other opioids and local anesthetics are commonly used [3]. Intrathecal opioid infusion, however, carries risks of fatal complications, as any sudden reduction of drug delivery due to device malfunction (pump or catheter failure) or programming errors carries significant risks of withdrawal [2]. Patients may also wish to explant their IDDS due to end of system lifespan, infection, surgical complications (pocket, catheter or pump related), granuloma, or lack of efficacy [2]. For patients wanting IDDS explantation, there are challenging considerations to facilitate a safe transition off opioid delivery.

2. Sublingual buprenorphine-naloxone microdosing induction protocol

We adopted a strategy to use an established microdosing protocol using sublingual buprenorphine-naloxone to safely facilitate IDDS explantation. Our dosing consisted of a 7-day titration regimen with a subsequent saline fill of the pump on the last day, as outlined in Table 1. The schedule was designed to provide adequate pain relief as well as prevent opioid withdrawal and respiratory depression. The saline fill maintains catheter patency and flushes any residual drug from the IDDS reservoir and catheter. This helps mitigate potential toxicity or withdrawal symptoms during the transition to oral medications.

After initiating the protocol, pain physicians use the Clinical Opiate Withdrawal Scale (COWS) to monitor for withdrawal symptoms and need of supplemental buprenorphine-naloxone. Patients reported no withdrawal symptoms and stabilized pain control in subsequent follow up visits.

In our experience, we successfully transitioned 4 patients off their IDDS. The patients were highly motivated and engaged throughout the process. Both during and following the protocol, they did not report any withdrawal symptoms (COWS score of 0) nor require supplemental non-opioid medications such as clonidine and benzodiazepines for withdrawal or anxiety symptoms.

3. Microinduction of buprenorphine-naloxone

Buprenorphine was initially developed as an analgesic, but with the addition of naloxone, the combination became popular as an effective opioid-replacement therapy [4]. Buprenorphine has unique pharmacological effects due to its (1) high affinity to μ-opioid receptors, (2) partial agonism that has low efficacy and prevents opioid withdrawal symptoms, (3) slow dissociation rate from μ-opioid receptors leading to prolonged duration of action, and (4) full k-opioid antagonism that dampens opioid induced dysphoric and psychotomimetic effects [4]. Naloxone is often compounded with buprenorphine as a sublingual tablet to minimize intravenous diversion, as naloxone is a competitive broad opioid receptor antagonist with limited oral bioavailability but higher intravenous bioavailability. At low doses, it can reverse opioid-induced respiratory depression, sedation and hypotension [4]. Thus, buprenorphine-naloxone's low abuse potential, favorable safety profile due to its ceiling effect on respiratory depression and fewer withdrawal symptoms renders it an effective first line medication for opioid agonist treatment in opioid use disorder [4].

Prior to administering buprenorphine-naloxone, patients are traditionally required to be in moderate opioid withdrawal from other opioids to avoid precipitated opioid withdrawal [5]. This is because buprenorphine displaces other opioids at the μ-receptor due to its high affinity, thus its partial agonism can precipitate withdrawal. A microdosing schedule was first introduced as the Bernese method, where patients start at low doses (Bernese method started at 0.2mg) of buprenorphine overlapping with opioid use and then have small repetitive dosing at sufficient intervals to not precipitate withdrawal. The buprenorphine slowly

Table 1
Buprenorphine-Naloxone Titration Regimen. Microdosing schedule of buprenorphine-naloxone to facilitate safe explant of IDDS system.

Day	Titration
1	0.5mg SL BID
2	0.5mg SL TID
3	1mg SL BID
4	2mg SL BID
5	2mg SL QID
6	4mg SL TID
7	12mg SL q daily and saline fill of IDDS

https://doi.org/10.1016/j.inpm.2023.100258
Received 12 April 2023; Received in revised form 17 May 2023; Accepted 18 May 2023

accumulates due to its high affinity and long half-life and eventually replaces the full μ-agonist at the receptors [5].

4. Conclusion

For patients with IDDS implants who are at risk of severe complications including opioid withdrawal from dose reduction, the process of transitioning patients from their IDDS can be challenging and uncertain. A microdosing protocol of buprenorphine-naloxone has been employed and reveals promise in transitioning patients off intrathecal opioids within a week without experiencing withdrawal symptoms.

Funding

The authors have no sources of funding to declare for this manuscript.

Consent

Both patients provided consent to report these cases.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Vishal Varshney reports a relationship with Abbott that includes: speaking and lecture fees and travel reimbursement. Vishal Varshney reports a relationship with Medtronic that includes: speaking and lecture fees and travel reimbursement. Vishal Varshney reports a relationship with Heron Therapeutics Inc that includes: speaking and lecture fees and travel reimbursement. Jill Osborn reports a relationship with Abbott that includes: speaking and lecture fees and travel reimbursement. Jill Osborn reports a relationship with Edwards Lifesciences Corporation that includes: speaking and lecture fees and travel reimbursement.

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