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From Rare to Reality: The Challenge of Controlling Pain in Patients on Buprenorphine in the Acute Care Setting

Timothy J Atkinson[1*], **Meredith Crumb**[2] **and Mena Raouf**[2]

[1]*Clinical Pharmacy Speciality, VA Tennessee Valley Healthcare System, Nashville, Tennessee, USA*

[2]*Pharmacy Practice, VA Tennessee Valley Healthcare System, Nashville, Tennessee, USA*

[*]**Corresponding author:** Timothy J Atkinson, Clinical Pharmacy Specialist, Pain Management Director, PGY-2 Pain and Palliative Care Pharmacy Residency, VA Tennessee Valley Healthcare System, Nashville, Tennessee, USA, Tel: +15186265000; E-mail: Timothy.Atkinson@va.gov

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Abstract

Prescription opioid use has increased dramatically in the past 20 years with prescriptions for opioids and overdoses both increasing by 400% in what is now being called an opioid epidemic. The CDC's Guidelines for Prescribing Opioids for Chronic Pain were released in March 2016 and the result has been increasing scrutiny of opioid prescriptions. For pain patients, this means minimizing opioid use and decreasing reliance, while others are being tapered off opioids altogether. Opioid tapers are predictably revealing unanticipated levels of opioid use disorder and unsupportable demand for enrollment in opioid assisted treatment (OAT) via buprenorphine/naloxone (Suboxone®) or methadone treatment programs. In July 2016, the Department of Health and Human Services released a final rule increasing prescribing limits of buprenorphine/naloxone (Suboxone®) to allow qualifying providers to treat up to 275 patients rather than capping panel size at 100. In addition to increased use in the treatment of opioid use disorder, there are new formulations of buprenorphine approved for chronic pain management. Therefore, while opioid use overall is decreasing, use of buprenorphine itself is dramatically increasing and introducing new challenges to treatment in trauma and acute pain settings based on its unique pharmacology. In recent years, case reports highlighting the challenge of managing pain when patients are treated with buprenorphine were published but until now were rarely seen in practice. It is, therefore, incumbent on all providers in these settings to become intimately familiar with buprenorphine and prepare to safely and effectively manage pain in these challenging patients.

Keywords: Buprenorphine; Acute pain; Opioid; Opioid resistance

Buprenorphine Overview

Buprenorphine was first introduced in 1978 as an injection for treatment of moderate to severe pain followed by the release of the sublingual (SL) tablets in Europe in 1982 [1-5]. It was later in 2000 when buprenorphine was approved by the United States Food and Drug Administration (FDA) for opioid dependence as part of the drug treatment act (DATA) [6,7]. Buprenorphine was co-formulated with naloxone and introduced into the market as Suboxone® in 2002 [8].

Buprenorphine Pharmacology

What makes buprenorphine an ideal choice for opioid assisted treatment? It is not because it is a partial agonist otherwise we could just use pentazocine or butorphanol [9]. It is not because of its long half-life, lipophilicity, or ceiling effect on respiratory depression within the therapeutic range [5,10]. Buprenorphine is valuable because it has unique binding kinetics that cumulatively result in the ability to displace other opioids, saturate opioid receptors, and block their effects for prolonged periods of time [5]. These factors together result in a strong defense that requires profound concentrations of naloxone or other opioids to overcome [5,11,12]. Additionally, buprenorphine is a potent kappa opioid receptor antagonist, which reduces stress-induced drug seeking and relapsing behavior [13,14].

Buprenorphine has unique pharmacologic properties that distinguish it from its dehydroxylated phenanthrene counterpart's hydrocodone, oxycodone, levorphanol, hydromorphone, oxymorphone, naloxone, and butorphanol [7]. Buprenorphine is a partial agonist at the μ-1 receptor with strong affinity and binding capacity, long terminal half-life, and slow and incomplete dissociation from the μ-receptor [5,7]. What is the impact of each property? Partial agonism means that when buprenorphine acts on the μ-receptor, it elicits a partial analgesic response. Simply speaking, buprenorphine is similar to pushing the gas pedal half way compared to a full agonist such as morphine that pushes the gas pedal all the way to the floor.

Buprenorphine has high affinity for opioid receptors and therefore has the ability to displace other opioids [5,7]. Buprenorphine competitively displaces other opioids and at clinical plasma concentrations has been found to displace therapeutic concentrations of fentanyl. Buprenorphine is very lipophilic and has a terminal half-life of 24-42 hours [7]. Buprenorphine slowly and incompletely dissociates from μ-receptors, with a dissociation half-life of 166 minutes and 50m binding after 1 hour [9]. Due to buprenorphine's high receptor affinity and incomplete dissociation from μ-receptor, it has been found to block the effects of morphine and persist undiminished for at least 25 to 30 hours after administration [15]. In fact, buprenorphine is so difficult to dislodge from opioid receptors that it takes 40 times the concentration of naloxone to displace compared to fentanyl [11].

Buprenorphine Products

Currently, there are several buprenorphine products available in the following formulations: tablets, sublingual, buccal, transdermal,

parenteral, and most recently as an implant. The newest formulation, Probuphine was FDA approved on May 26, 2016 and is the first buprenorphine implant for the maintenance treatment of opioid dependence [15,16]. The ethylene vinyl acetate implant contains 74.2 mg buprenorphine, equivalent to 80 mg buprenorphine HCl. The implant is designed to provide a constant, low-level dose of buprenorphine for six months in patients who are already stable on low-to-moderate doses of other forms of buprenorphine. Other buprenorphine formulations that are FDA approved for treatment of opioid dependence include Subutex® (SL), Suboxone® (SL, film), Zubsolv® (SL), and Bunavail® (buccal), the latter 3 of which are co-formulated with naloxone [7,8,17,18]. FDA approved buprenorphine products for pain include Buprenex® (injection), Butrans® (transdermal), and Belbuca™ (buccal) [19-21]. Belbuca™ is dosed every 12 hours and is available in the following dosing strengths: 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg [10]. Butrans® patch is available as 5 mcg/hour, 10 mcg/hour, and 20 mcg/hour strengths and is changed every 7 days [11].

The numerous buprenorphine products and indications for both substance abuse and chronic pain increases the likelihood of encountering a patient in an acute trauma that may have buprenorphine in their system raising the issue: how does this impact the acute management of pain in patients chronically exposed to buprenorphine?

Management of Acute Pain in Patients on Buprenorphine

Managing acute pain in trauma patients who are receiving buprenorphine is a clinical dilemma. The first widely accepted approach is to target alternative pain pathways and optimize the use of adjunct therapies including non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. ketorolac or ibuprofen), gabapentinoids (i.e. gabapentin or pregabalin), ketamine, serotonin-norepinephrine reuptake inhibitors (SNRIs), etc. [22-26]. Perhaps the safest approach is avoiding opioid receptors and utilizing anesthesia services to perform a regional block, however, due to short-term efficacy this may not be feasible in many acute care settings.

Although buprenorphine is a partial opioid agonist, it elicits an analgesic response [5,27-30]. However, the way it is dosed in treating opioid dependence with once daily dosing is not optimal to provide analgesia. The main reason is that while buprenorphine's elimination half-life is 26-42 hours, its duration of analgesia is 6-8 hours [5,22,27-30]. One approach to circumvent this is to divide the daily dose of buprenorphine and administer every 6 to 8 hours [22,27-30]. For example, a patient on buprenorphine 24 mg daily would receive 6 mg every 6 hours.

Buprenorphine is available parenterally for intramuscular (IM) and intravenous (IV) administration and is FDA approved for acute pain [21]. Several studies have shown that buprenorphine given parentally in the post-operative setting is similarly effective to morphine often with a longer duration of action [31-39]. Parenteral 0.3 mg buprenorphine has been found equivalent to the analgesic effects of 10 mg of parenteral morphine [39]. A pharmacokinetic advantage of parenteral buprenorphine is significantly faster onset compared to non-parenteral formulation (ex: buccal, sublingual). Following sublingual dosing, the time to peak plasma concentration is 3.3 hours whereas, with IM administration, peak plasma concentrations are rapidly achieved with analgesic effect observed within 15 minutes and peak effect at 1 hour [21,40]. When used IV, the times to onset and peak effect are shorter [21]. The analgesic effect with parenteral buprenorphine persists for 6 hours or longer and can be dosed every 6 to 8 hours. Therefore, parenteral buprenorphine is an attractive, but often overlooked option, to manage acute pain for patients already maintained on buprenorphine. This approach may allow improved analgesic response despite its partial agonism and together with adjunct approaches may provide sufficient relief. If unsuccessful, however, this approach results in prolonging the time required for buprenorphine's opioid blocking effects to fade.

If parenteral buprenorphine is not available or the clinician chooses to use a full opioid agonist, some literature recommends using high doses of short acting opioids [22,41-44]. In theory, using short-acting opioids in high doses will achieve high concentrations and may compete with buprenorphine for the μ-receptor. Many of these studies utilized morphine, fentanyl, hydrocodone, and oxycodone by various administration routes and/or patient controlled analgesia (PCA). Using a PCA would require repeated boluses in addition to basal administration to attain higher concentrations.

Building a concentration gradient favoring a pure opioid agonist may be effective depending on the formulation of buprenorphine. For example, a patient on Suboxone® 2 mg daily or on a buprenorphine product for pain such as Belbuca™ or Butrans®, may be initiated on a short acting opioid while continued their home buprenorphine dose. Achieving analgesia with short acting opioids in patients on higher doses of buprenorphine may not feasible due to buprenorphine's pharmacologic properties. Buprenorphine exhibits dose-related receptor occupancy at the μ-receptor where 2 mg, 16 mg, and 32 mg doses occupy 24% to 47%, 85% to 92%, and 94% to 98% of the μ-receptors, respectively [45]. Because of buprenorphine's tight binding at the μ-receptor with slow and incomplete dissociation, it would be difficult to displace receptor-bound buprenorphine with administering short-acting opioids [5,9,11]. If such a strategy were necessary, utilizing a medication with similar lipophilicity and potency such as fentanyl would be logical but this has not validated in clinical trials.

If buprenorphine is discontinued and high dose opioid therapy is being utilized to challenge receptor occupancy, then more opioid receptors will become available as buprenorphine levels drop over several days. A corresponding decrease in opioid therapy utilized for challenge is critical to avoid overdose. This is a precarious balance in shifting drug levels that would make any practitioner nervous about utilizing this strategy if another option is available. It is recommended that the patient be monitored closely during these 24-72 hours with a standing order for naloxone, a μ-opioid antagonist, which is used clinically to displace pure opioid agonists to reverse overdose.

Increasing prevalence and widespread use of buprenorphine is an indicator of how critical it is for providers to recognize the unique challenges that patients on buprenorphine represent in the acute care or trauma setting. At best, pain control in these patients will be challenging and in some cases they will require non-traditional methods to avoid patient suffering and delivery of high quality individualized and evidenced-based care.

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