Buprenorphine

New Tricks With an Old Molecule for Pain Management

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Abstract: Sublingual buphrenorphine is a unique opioid medication based on its pharmacokinetics and pharmacodynamic properties. It may be used "on label" as an alternative choice to methadone for the treatment of opioid addiction or "off-label" for the treatment of both acute and chronic pain. Because of high μ receptor affinity and resultant blockade, it has been suggested that this might interfere with the management of moderate to severe pain in patients on opioid agonist treatment. The following article will offer strategies and approaches to address some of these real and perceived challenges.

Key Words: S/L buphrenorphine, addiction, acute pain, chronic pain

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Sublingual (S/L) buprenorphine has a well-established role in the treatment of the disease of opioid addiction but is regaining popularity in the role of a primary analgesic. S/L buprenorphine, like methadone, can be used for the dual purpose of treating the disease of addiction and pain, but it poses an interesting challenge for the prescriber. For appropriate prescribing of this medication, the unique pharmacokinetic/pharmacodynamic aspects of buprenorphine must be understood, allowing for proper patient selection and evaluation to optimize treatment outcomes in the treatment of pain, addiction, or the comorbid condition of pain and addiction.

Pain in patients with the disease of addiction being present is not common, but healthcare professionals must understand that pain can present in more than 1 way and can be treated in more than 1 way.

This article will discuss the ways that pain can present and provide guidelines for healthcare professionals to optimize treatment of patients with pain who are on opioid agonist therapy (OAT) with S/L buprenorphine with or without naloxone (Suboxone or Subutex) illustrated with clinical case studies.

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PHARMACOLOGY OF BUPHRENORPHINE

Buprenorphine (Fig. 1) is a semisynthetic highly lipophilic opioid that is a derivative of the morphine alkaloid thebaine.[1,2] Its primary activity in man seems to be that of a partial agonist at the μ opioid receptor and as an antagonist at the κ receptor.[3–7] The effects of binding at μ opioid receptors include supraspinal analgesia, respiratory depression, and miosis. Buprenorphine's antagonist effects at the κ receptor are associated with limited spinal analgesia, dysphoria, and psychotomimetic effects.[8]

Buprenorphine, being a partial μ opioid agonist, may have a wider safety profile compared with other full μ agonists, especially with regard to respiratory depression. Further, the slow dissociation of buprenorphine from the μ and κ opioid receptors may result in fewer signs and symptoms of opioid withdrawal upon termination of buprenorphine therapy than those that occur with full μ opioid agonists, such as morphine, heroin, and methadone.[9]

Buprenorphine has high affinity at the μ opioid receptor that may offer a "blockade effect" to other opioids that typically lasts in excess of 24 hours,[9] making once-daily or even longer dosing possible for the treatment of opioid addiction. Effective analgesia is achieved at relatively low receptor occupancy of 5% to 10%.[10] The degree of analgesia seems not to be related to plasma concentration of the drug because the dissociation at the receptor site lags behind plasma concentration.[9] Buprenorphine is at least 30 to 40 times more potent than morphine over its linear range,[11–13] with an analgesic effect seen over the 0.1 to 10 mg range.[14] As a partial agonist, the buprenorphine-morphine equivalence at higher doses becomes less certain due to a flattening off of the agonist curve.[15] In the clinical experience of the authors, buphrenorphine, like methadone, is dosed three times a day before (t.i.d.) or four times a day before (q.i.d.) for pain. However, it should be noted that this dosing schedule for sublingual buphrenorphine for analgesia is not documented in the peer review literature.

As a result of buprenorphine's high receptor site affinity, it may interfere with effectiveness of other full μ analgesics. As with other partial μ agonists, buprenorphine is contraindicated in opioid-dependent patients because it may precipitate severe withdrawal.[16,17] Because

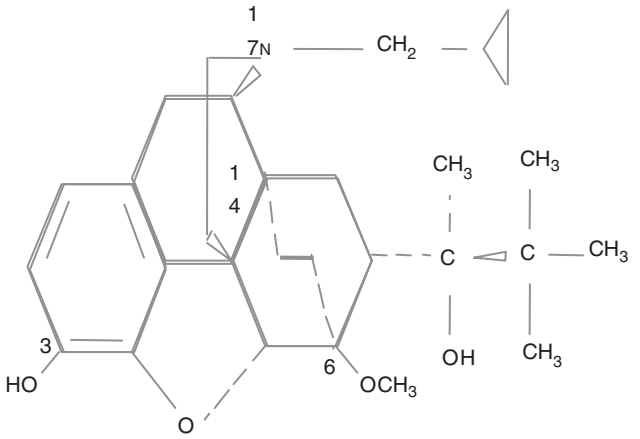

FIGURE 1. Molecular structure of buprenorphine. Adapted from: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. McGraw-Hill. 9th ed.

it is a partial agonist, it effects plateau at higher doses, and it begins to behave more like an antagonist.[18] This antagonist property in higher doses limits the dose-dependent analgesic effect and respiratory depression.[17] The high-affinity blockade significantly limits the effect of subsequently administered opioid agonists or antagonists, and the "ceiling effect" confers a high safety profile clinically, a low level of physical dependence and often mild withdrawal symptoms on cessation after prolonged administration when compared with methadone.[19]

Oral bioavailability of buprenorphine is low because of extensive first-pass hepatic metabolism.[20,21] The administration of buprenorphine by the sublingual route allows for bypassing of the first-pass hepatic metabolism thus increasing bioavailability. Buprenorphine is well absorbed sublingually, with 60% to 70% of the bioavailability of intravenous doses.[22] The drug is widely distributed, with a peak plasma concentration at approximately 90 minutes and a half-life of 4 to 5 hours.[23]

Buprenorphine is lipophilic, and brain tissue levels far exceed serum levels. It is highly bound to plasma protein and is inactivated by enzymatic transformation via N-dealkylation and conjugation.[8] Buprenorphine is mainly metabolized to inactive conjugated metabolites (80% to 90%), but nor-buprenorphine, a product of N-dealkylation by the cytochrome P-450 3A4 enzyme, has more potent respiratory depressive effects than the parent drug.[24,25] There are drugs that interfere with the 3A4 system, such as certain antibiotics, antifungal and HIV protease inhibitors, that could decrease production of nor-buprenorphine. Conversely, there are drugs that induce the 3A4 system, such as phenobarbital and certain antiseizure medications that could increase the levels of nor-buprenorphine.[26,27] The clinical implications of these interactions are unknown.

S/L BUPRENORPHINE

The buprenorphine-containing products Suboxone and Subutex are the only 2 Schedule III drugs currently approved for the treatment of opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000).[28] DATA 2000 allows office-based opioid treatment with buprenorphine with or without naloxone. The prescriber must be a certified and specially trained physician who has received a *waiver* from the requirement to register as a narcotic treatment program from the Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMHSA).[28] Complete information on obtaining the waiver for the use of S/L buphrenorphine for office-based opioid treatment can be accessed on the following government web site: http://buprenorphine.samhsa.gov/fulllaw.html.

The combination product Suboxone is available in 2 and 8 mg tablets combined with naloxone at 0.5 and 2 mg, respectively, whereas the mono product Subutex is available without naloxone. Naloxone is poorly absorbed via the sublingual route but precipitates withdrawal symptoms if administered parenterally to an opioid-dependent person, thereby potentially reducing the risk of parenteral misuse and diversion.[11,29]

In as much as buprenorphine alone as a partial agonist will precipitate opioid withdrawal in active opioid-dependent users, the addition of naloxone to buprenorphine as an abuse deterrent has been questioned on its pharmacologic merits.[30] However, it is thought by some that the addition of naloxone to buprenorphine might attenuate the "high" derived from the parenteral misuse of the sublingual product thereby reducing the abuse liability by the parenteral route.[31]

The off-label use of S/L buprenorphine (Suboxone/Subutex) for the treatment of pain is *not* prohibited under Drug Enforcement Administration requirements.[32] One does not need a waiver from the CSAT, but only a valid license to prescribe a Schedule III controlled substance.[32] In addition, the prescriber should *not* place an X before his/her dea registration number. To prevent any confusion about the off-label use of S/L buphrenorphine by the patient or dispensing pharmacist, the authors suggest the prescriber write on the prescription: "Chronic Pain Patient" and "Off-Label Use." Although this is not required by state or federal regulations, it eliminates any doubt about the purpose of the prescription.

PAIN

How to treat a patient for pain who is using S/L buprenorphine for the disease of addiction requires an individualized approach depending on the category his or her pain falls into. Pain can be categorized as anticipated acute pain, unanticipated acute pain, acute pain superimposed on chronic pain, or chronic pain.

The literature suggests that to treat pain in a patient on OAT with S/L buphrenorphine one must discontinue the S/L buphrenorphine and do a reinduction if the pain syndrome resolves.[33] This may not be necessary in some instances as noted in the following clinical case studies. In certain circumstances patients may be spared the dis-

comfort of having to go into withdrawal as the full μ agonist is discontinued and they are rotated back to S/L buphrenorphine.

In all the case studies, appropriate treatment plans were established consistent with Universal Precautions in Pain Medicine[34,35] with interval prescribing of all pain medications (Table 1).

Patient-centered urine drug testing (UDT) was part of the treatment protocol.[36,37] Two types of UDT were performed on each specimen: immunoassay testing for drugs of abuse, which if positive was followed by confirmation testing by gas chromatography/mass spectrometry to identify specific drugs or their metabolites, and gas chromatography/mass spectrometry only to identify semisynthetic or synthetic opioids. The UDT for buprenorphine was not performed due to the expense of the assay.

ANTICIPATED ACUTE PAIN

Painful procedures such as elective surgery can be anticipated. This affords both the patient and the treatment team the opportunity to plan and so optimize the management of this acute pain. If the elective procedure is associated with mild to moderately severe pain and the patient is not NPO, buphrenorphine can be used. In most cases, the pain can simply be managed by titrating the sublingual dose upward to effect with a t.i.d. or q.i.d. dosing regimen.

If breakthrough medication is needed, consider using one with high potency such as oral transmucosal fentanyl lozenge, fentanyl buccal tablets, or hydromorphone. Demerol (meperidine) is a particularly poor choice due to its anticholinergic and histaminergic qualities and the accumulation of the potentially toxic metabolite (normeperidine). Normeperidine is a potent central nervous system irritant that can lead to confusion, disorientation, hallucinations, headaches, and even seizures once individual tolerances are exceeded.[38,39] As a result, the American Pain Society has recommended that meperidine should not be used on a chronic basis.

Normeperidine may be used for acute pain. However, buprenorphine has a "blockade effect" compared with other opioids because of its high affinity at the μ opioid receptor.[9] This high affinity at the μ opioid receptor would result in normeperidine not being an effective choice for breakthrough medication with the concomitant use of S/L buphrenorphine.

It is important to note that although the addition of a partial μ agonist to a fully μ-dependent patient may precipitate severe withdrawal, the reverse is not true. Although analgesic response may be blunted, full μ agonists can always be added to buprenorphine-maintained patients without fear of precipitating withdrawal. Care however should be exercised during titration due to potentially unpredictable μ sensitivity.

TABLE 1. The 10 Principles of "Universal Precautions"

1. Diagnosis with appropriate differential
2. Psychologic assessment including risk of addictive disorders
3. Informed consent (verbal vs. written/signed)
4. Treatment agreement (verbal vs. written/signed)
5. Pre/postintervention assessment of pain level and function
6. Appropriate trial of opioid therapy ± adjunctive medication
7. Reassessment of pain score and level of function
8. Regularly assess the "Four A's" of pain medicine Analgesia, Activity, Adverse reactions, and Aberrant behavior
9. Periodically review pain and comorbidity diagnoses, including addictive disorders
10. Documentation

See also *Pain Med.* 2005;6:107–112[34] for related information.

Clinical Case Study

K.C. is a 24-year-old woman who presented with a problem list that included addiction to Percocet, with anxiety and depression. The patient had multiple episodes of opioid prescription drug fraud. She stated the "If it rained Percocet I would be very happy." She was inducted and stabilized on 16 mg of Subutex along with appropriate treatment for her comorbid conditions. After 6 years the patient had a traumatic injury that resulted in a tear of her posterior tibial tendon that did not respond to conservative treatment and required operative repair. The patient had the operation with the anesthesiologist doing her in-patient pain management with a patient controlled analgesia pump of fentanyl. The dose of Subutex was increased to 8 mg t.i.d. At discharge the patient was prescribed hydromorphone 2 mg up to 4/d for 6 weeks postoperatively. Shortly afterward, she went back to her former dose of 16 mg of Subutex. The patient had multiple UDTs that were all appropriately negative and positive as per her prescribed medications. In addition, all her pill counts with each visit were as expected. The patient continues to work her successful program of recovery.

UNANTICIPATED ACUTE PAIN

Unlike anticipated pain, when the patient may be optimized before the elective procedure, some patients may experience unanticipated pain such as is seen with trauma or other acute, surgical emergencies. The patient may have mild to moderate pain that may be adequately managed with divided dosing of the maintenance drug. Titration to effect, up to 8 mg t.i.d. to q.i.d. may adequately manage the acute pain. In this case, breakthrough medicine such as oral transmucosal fentanyl lozenge, fentanyl buccal tablets, or hydromorphone may be used during this acute period.

If the patient is NPO then buprenorphine may not be an optimal choice as an analgesic. Although it is reasonable to think S/L buprenorphine can be used in this clinical situation, the buccal absorption of the drug may be unpredictable. The average systemic bioavailability of S/L buprenorphine is approximately 55%, with large intersubject variability.[20] A clinical trial should be considered to determine if buprenorphine would be effective if the patient is NPO.

Clinical Case Study

B.R. presented as 42-year-old man with 25-year history of polysubstance addiction with misuse of controlled-release oxydone as his drug of choice. He was induced and stabilized on Suboxone 2/0.5 mg 2 tablets once a day. The patient does physical labor installing dry wall. He had an accident that resulted in acute injury to his wrist with a deep laceration. He was treated as an out-patient and his Suboxone 2/0.5 mg was increased to q.i.d. for 1 week. The patient continues to work his successful program of recovery with UDT appropriately negative.

ACUTE PAIN SUPERIMPOSED ON CHRONIC PAIN

One assumes buprenorphine in divided doses was controlling pain for a patient with mild to moderate chronic pain. If that patient then has acute pain superimposed, an immediate release/rapid-onset opioid with high receptor site affinity and potency such as oral transmucosal fentanyl lozenge, fentanyl buccal tablets, or hydromorphone can be added. Then one would titrate to effect to treat the acute pain with the immediate release/rapid-onset opioid.

Clinical Case Study

S.T. is a 59-year-old woman with a history of fibromyalgia, degenerative joint disease secondary to "osteoarthritis" and peripheral neuropathy of unknown etiology. She denied any history of drug misuse or addiction. However, her UDT was inappropriately positive for hydrocodone, hydromorphone, and barbiturates. Some of the illicit medications were obtained through the Internet and some through doctor shopping. A meeting with the patient to determine the *motivation* behind her *behavior*[40] with her husband took place. After further evaluation the primary diagnosis of addiction was established with a secondary diagnosis of chronic pain. She was induced and stabilized on Suboxone 8/2 mg at $\frac{1}{2}$ tablet q.i.d. Six months later she had cervical spinal fusions at C_3-C_6. The patient had the operation with the anesthesiologist doing her in-patient pain management with a patient controlled analgesia pump of fentanyl. The dose of Subutex was not changed. At discharge the patient was prescribed hydromorphone 2 mg up to 4/d for 4 weeks postoperatively. The patient had multiple UDTs that were all appropriately negative and positive as per her prescribed medications. In addition, all her pill counts with each visit were as expected. The patient continues to work her successful program of recovery.

CHRONIC PAIN

Patients on S/L buprenorphine will, in the majority of cases, take the full dose of their medication once per day. For a chronic pain patient on S/L buprenorphine, one may divide the total dose and give it on a t.i.d. or q.i.d. dosing schedule. Then like any other chronic pain patient, the buprenorphine is titrated to effect.

In the authors' opinion, buprenorphine for chronic pain management has a 6 to 8 hours analgesic duration of action and therefore should be dosed t.i.d. or q.i.d. for optimum analgesic effect. There is no reference in the peer review literature on the analgesic duration of S/L buprenorphine. Once-daily dosing may provide >24 hours of relief in some patients, especially those who are suffering from withdrawal-mediated pain associated with short-acting, immediate-release opioids.

As a partial agonist, the effective dose is limited for acute or chronic pain treatment: 6 to 8 mg in a t.i.d. or q.i.d. dosing schedule (up to 32 mg/d total) is probably the maximum daily dose. If the maximum dose does not effectively reduce the pain, one can rotate to a full μ agonist in this patient population in compliance with federal regulations for prescribing a control substance.[32] For example, S/L buprenorphine dose at a μ equivalence of 8 to 24 mg is equal to $\sim$20 to 100 mg equivalents of methadone.[41] Although data in the literature are limited, and often based on single-dose studies, incomplete cross tolerance alone necessitates a conservative approach to any opioid rotation involving methadone.[41,42]

Clinical Case Study

W.C. is a 55-year-old woman with a polysubstance addiction with her drug of choice Morphine Sulfate Contin, which was chewed. She obtained her opioids via doctor shopping. She said, she did this to treat her pain secondary to 8 shoulders operations. She was induced and stabilized on 1 tablet Suboxone 2/0.5 mg q.i.d. This dosing schedule eliminated her cravings for illicit use of opioids and reduced her shoulder pain; her scores went from 6 to 1 or 2. The patient continues to work her successful program of recovery with UDT appropriately negative.

CONCLUSIONS

With an understanding of the pharmacokinetics and pharmacodynamics of S/L buphrenorphine, healthcare professionals can use this drug to treat their patients who have pain, the disease of addiction, and the comorbid conditions addiction and pain. Accepting inadequate pain relief for any patient, including those being treated with S/L buprenorphine is neither appropriate nor necessary.

It is the hope that the recommendations in this article for the treatment of pain patients who are on OAT with S/L buphrenorphine will be the impetus for long-term prospective studies. Until these studies are available, the treatment of pain will be both the "art" and "science" of medicine with the former playing a larger role.

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