REVIEWS

Buprenorphine as an Alternative for Treatment of Opioid Dependence

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Abstract

Besides its use as an opioid analgesic, buprenorphine is now becoming more favorable, as compared with methadone, to be used as an opioid maintenance agent in the treatment of opioid dependence. Several clinical studies have demonstrated that buprenorphine can be as effective as methadone in opioid maintenance treatment and has some advantages over methadone. With its partial agonist profile, buprenorphine has been proved to have high safety profile, low abuse potential, and low physical dependence. Considering that treatment of opioid dependence will require long-term commitment, all those properties of buprenorphine may determine whether a successful treatment can be achieved. This article will review pharmacology of buprenorphine, including cross-tolerance, physical dependence potential, its clinical efficacy and its safety profile as well as a review of how to use buprenorphine as a maintenance therapy for opioid dependence.

Key words: Buprenorphine, opioid dependence
Buprenorphine ทางเลือกใหม่สำหรับการรักษาผู้ป่วยติดยาเสพติดชนิดโอปิออยด์

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บทคัดยอ

นอกเหนือจากการใช้เป็นยาแก่ปวดแล้ว ปัจจุบัน buprenorphine กำลังได้รับความนิยมมากขึ้นเรื่อยๆ เนื่องจากมันมีแนวโน้มในการใช้รักษาผู้ป่วยติดยาเสพติดชนิดโอปิออยด์ (opioid dependence) การศึกษาทางคลินิกได้แสดงให้เห็นถึงประสิทธิภาพของ buprenorphine ที่เทียบเท่ากับการใช้ methadone รวมถึงช่วยได้รับประโยชน์ทางคลินิกมากขึ้นในผู้ป่วยที่มีประวัติการใช้ยาเสพติดที่คืบหน้ามากกว่า ด้วยคุณสมบัติเป็น partial agonist ของ buprenorphine ทำให้มีความปลอดภัยจากอาการเมตาสหรับการใช้ยา ส่วนในทางที่ผ่านมา ที่มีโอกาสมีการเกิดขึ้นมากกว่า อย่างไรก็ตามการใช้ buprenorphine อาจเป็นตัวทำนองว่าการรักษาจะได้ผล หรือไม่ ขึ้นอยู่กับการใช้งานอย่างมีประสิทธิภาพของ buprenorphine, การทดสอบแบบ cross-tolerance, โอกาสการติดยา (physical dependence potential), ประสิทธิผลทางคลินิก (clinical efficacy) และความปลอดภัยจากการใช้ยา (safety profile) รวมถึงวิธีการใช้ buprenorphine ในการรักษาผู้ป่วยติดยาเสพติดชนิดโอปิออยด์ (buprenorphine maintenance therapy for opioid dependence)

คำสำคัญ : Buprenorphine, opioid dependence
Over the past years, there have been only two types of medications for the treatment of opioid dependence. The first type is agonist substitution therapy (i.e. methadone). The second type is antagonist therapy (i.e. naltrexone), which unlike agonist therapy, naltrexone does not produce morphine-like agonist effects. Instead, it blocks agonistic effects. Both types have been effective in reducing illicit opioid use. However, both therapies have some pitfalls. Methadone, the standard substance in the substitution therapy of opioid dependence, still has high abuse potential and high level of physical dependence, whereas naltrexone has difficulty to retain patients in treatment due to its lack of desired positive agonistic effects.

With the discovery of multiple opioid receptors, newer opioid analgesics (mixed agonist/antagonists) have been developed to take advantage of the pharmacologic effects mediated by these receptors. This development effort has been aimed primarily at reducing the abuse potential and physical dependence property of these medications, while maintaining analgesic efficacy. Buprenorphine is one of those newer opioid analgesics. It has high affinity at both mu and kappa opioid receptors. It is a partial agonist at mu opioid receptor but acts as an antagonist at kappa opioid receptor. This unique pharmacologic profile has provided an opportunity to develop an alternative treatment for opioid dependence.

**Pharmacology of Buprenorphine**

**Pharmacokinetics**

For the treatment of opioid dependence, it is very important that injectable forms of administration be avoided. Otherwise, this can lead to the spread of infectious diseases such as HIV, hepatitis and other parenterally transferred infections. Since buprenorphine is less well absorbed when taken orally, and is quickly metabolized by the liver, known as the “first pass effect”, sublingual administration has been the primary route used in studies of clinical efficacy for treating opioid dependence. When taken sublingually, buprenorphine is well absorbed with 60-70% of the plasma concentration achieved by the parenteral route. The drug is widely distributed throughout the body with a peak plasma concentration at approximately 90 minutes and a half life of 4 to 5 hours. Buprenorphine is highly bound to plasma proteins. It is highly lipophilic and brain tissue levels far exceed serum level. Buprenorphine is metabolized in the liver by the CYP450 3A4 enzyme system. It undergoes N-demethylation and conjugation. Buprenorphine's metabolite, norbuprenorphine, has more potent respiratory depressive effects than the parent drug, although the analgesic effect of norbuprenorphine is one-fiftieth that of buprenorphine following intravenous administration. At present, there is no evidence that norbuprenorphine activity is responsible for effects observed in the treatment of opioid dependence. Because of its high lipid solubility, buprenorphine is also expected to be active by intranasal route.

**Pharmacodynamics**

Buprenorphine, generally described as a mixed agonist/antagonist opioid, is a semi-synthetic opioid derivative of the thebaine. It acts as a partial agonist at the mu opioid receptor, characterized by a reduced intrinsic activity compared to the pure agonist. Buprenorphine also has the properties of a weak kappa opioid receptor antagonist (i.e. it does not show any intrinsic activity on this receptor but can block agonistic effects). Clinically, the effects of buprenorphine are primarily expressed through the mu opioid receptor and are similar to those of full agonists like morphine and methadone. Because it is a partial agonist, its effects plateau at higher doses, and it begins to behave more like an antagonist. This antagonistic activity in higher doses limits the maximal analgesic effect and respiratory depression. This a so-called “ceiling effect” confers a high safety profile, a low level of physical dependence and only mild withdrawal
symptoms upon cessation after prolonged administration. These qualities make it advantageous for the treatment of opioid dependence. Moreover, slow dissociation from the opioid receptor of buprenorphine provides a long duration of action, which allows dosing schedules to be varied from several times daily to several times weekly.

Although buprenorphine alone, taken in the form of a sublingual tablet, is efficacious and possesses other desirable therapeutic characteristics (i.e. high safety profile and low level of physical dependence), a combination containing buprenorphine and naloxone has been developed in order to decrease abuse and misuse. The addition of naloxone, whose sublingual bioavailability is poor, results in only buprenorphine effect when the combination tablet is taken by the therapeutic (i.e. sublingual) route. However, if the combination is injected, the naloxone effect precipitates opioid withdrawal, thus deterring intravenous abuse. The issue of limiting buprenorphine’s abuse liability with naloxone is complicated by the fact that naloxone does have some sublingual bioavailability. Thus, the buprenorphine : naloxone ratio must be chosen carefully in order to avoid naloxone effects when the combination is used as intended. It was determined that the optimum combination is a 4:1 ratio of buprenorphine to naloxone and tablets containing 2/0.5 and 8/2 mg of buprenorphine/naloxone have been developed.

**Cross-tolerance**

Tolerance, defined as a decreasing effect of a given drug following chronic administration of that drug, normally is a problem when opioids are used as analgesic agents. When they are used for the treatment of opioid dependence, however, it is an advantage. For example, tolerance to methadone maintenance therapy develops cross-tolerance to other opioid drugs such as heroin, and this helps reduce illicit drug use since heroin abuser will no longer entertain the positive effects, which if not due to methadone cross-tolerance, would occur from the use of heroin. In the case of buprenorphine, due to its unique pharmacological profile, reducing illicit drug use may be through the development of cross-tolerance or through pharmacological antagonism.

**Buprenorphine-induced physical dependence**

Although having low intrinsic activity at mu opioid receptor, buprenorphine does produce physical dependence as demonstrated by the ability of pure opioid receptor antagonists (i.e. naloxone and naltrexone) to precipitate an opioid withdrawal in patients maintained on buprenorphine. The physical dependence, however, is considered to be low, as when compared to patients maintained on a full mu agonist such as methadone, higher doses of the opioid antagonist naloxone are necessary to precipitate withdrawal in patients maintained on buprenorphine. Clinically, spontaneous buprenorphine withdrawal symptoms can be observed after several days following abrupt cessation of buprenorphine treatment and is usually described as mild to moderate in intensity. The symptoms include runny nose, watery eyes, hot flashes, lethargy, nausea, diarrhea, restlessness, and irritability. Gradual reduction, rather than abrupt termination of buprenorphine would likely result in no opioid withdrawal symptoms.

**Clinical efficacy of buprenorphine**

A series of controlled clinical studies firmly established the clinical efficacy of buprenorphine. Some of the study were designed to compare buprenorphine to placebo, either to “active” or “inactive” placebo, and others compared buprenorphine to methadone. Retention in treatment and abstinence from illicit opiate use (commonly assessed by urine toxicology) were utilized as primary outcome measures of success, but other measures, such as request for dose changes, withdrawal symptoms and reduced heroin craving were also employed.

**Buprenorphine versus placebo**

In a double-blind trial designed to assess the early clinical effectiveness (1-2
weeks) of buprenorphine compared with placebo, subjects were randomly assigned to receive either 2 mg/day or 8 mg/day buprenorphine or placebo over a period of 14 days. Between day 6 and 13, the subjects were then given the option of receiving an altered dose. A randomization was then carried out to one of the other two treatment groups to which the subjects did not belong. The alternate dose then had to be taken up to and including day 14. The results showed that subjects treated with buprenorphine, irrespective of their dose, requested fewer dose changes, used less illicit opiates and reported higher ratings of medication adequacy than those treated with placebo.

Two other studies that compared the buprenorphine and placebo also showed higher maintenance rates and less illicit opiate use in subjects treated with buprenorphine.

In another randomized, double-blind study designed to evaluate the safety and efficacy of 8 mg/day buprenorphine compared with 1 mg/day buprenorphine in maintenance treatment of opioid dependence, subjects were treated with buprenorphine over a period of 16 weeks. Since the administration of placebo to patients who are addicted to drugs is regarded as unethical, a dose of 1 mg/day buprenorphine was regarded as an “active” placebo. The results showed that subjects treated with 8 mg/day buprenorphine had higher maintenance rates and less illicit opiate use than those treated with 1 mg/day buprenorphine.

Similar results were observed in several other studies, in which subjects treated with 8 mg buprenorphine showed higher retention rates than those treated with 1 mg or 3 mg buprenorphine.

**Buprenorphine versus methadone**

In a double-blind study with a comparison of parallel groups, subjects were randomly assigned to receive 8 mg/day buprenorphine, 20 mg/day methadone, or 60 mg/day methadone. In term of maintenance rates and the percentage of opiates-negative urine, buprenorphine showed significant superiority compared to 20 mg/day methadone and an equivalence compared to 60 mg/day methadone. The results were similar to that of a further study, in which the subjects could changes their own dose until achieving an optimal dose response following an initial stabilization at buprenorphine 8 mg/day or methadone 50 mg/day. The mean maintenance dose was 8.9 mg/day buprenorphine and 54 mg/day methadone. Both drugs were effective on measures of treatment retention and opiate-free urine. These results were further confirmed by a study with similar flexible dosage protocol. This variable dose study resulted in a mean stabilization buprenorphine dose of 10.5 mg/day and in a mean stabilization methadone dose of 69.8 mg/day. The percentage of opioid-free urine and heroin craving scores were similar in both groups, although retention rate was significantly better in the methadone group.

Similar results could also be observed in several other studies. A 17-week, double-blind study showed that 7-14 mg/day buprenorphine and high dose (60-100 mg/day) methadone were equally effective in term of maintenance rate and the percentage of opioid-free urine. Both high dose methadone and 7-14 mg/day buprenorphine were superior to low dose (20 mg/day) methadone. A recent published study compared the efficacy of buprenorphine and methadone in the treatment of opioid dependence. The results showed that 9.2 mg/day buprenorphine and 81.5 mg/day methadone were equally effective in term of retention in treatment at 12 weeks.

In contrast, better maintenance rates for methadone were demonstrated by other studies. This could be due to the relatively low dose (2, 4 and 6 mg/day) of buprenorphine utilized in comparison with appropriate dose (65 mg/day) of methadone. Better maintenance rates for methadone were also observed in a study, in which an appropriate dose of 8 mg/day buprenorphine was compared to relatively high dose (80 mg/day) methadone.

**Safety profile**

Because buprenorphine is a partial agonist with relatively low intrinsic activity, it
should limit life-threatening respiratory depression, contributing to a safety profile that is better than that of methadone, a full mu opioid agonist currently used in the treatment of opioid dependence. For example, when buprenorphine was administered to non-dependent individuals, respiratory depression was increasingly related to buprenorphine dose over a range of 1-4 mg, but this dose effect began to level out at higher doses; administration of 32 mg buprenorphine produced no greater respiratory depression than that produced from 16 mg buprenorphine. The safety of buprenorphine may be even greater in opioid-tolerant individuals, as supported by studies showing that buprenorphine-dependent subjects can receive substantially higher doses than their usual maintenance doses without signs of toxicity. For example, administration of 16 mg buprenorphine in patients normally getting 8 mg buprenorphine daily produced no adverse effect. The most compelling evidence for the excellent safety of buprenorphine may come from the fact that there is almost no lethal overdose cases associated with respiratory depression produced by buprenorphine alone, despite the extensive use of buprenorphine as an analgesic. Buprenorphine has been approved for the treatment of opioid dependence in France since 1996 (currently, it has also been approved in Australia in 2001 and in the US in 2002), a series of overdose deaths were reported. The vast majority of these cases resulted when buprenorphine and benzodiazepines were concomitantly abused via the parenteral route. When compared to methadone, the death rate from buprenorphine overdose is still far less; the estimated risk of overdose death is at least 5 times higher for methadone than for buprenorphine.

Some considerations before getting start on buprenorphine

Because buprenorphine is a partial mu opioid agonist and consequently has low intrinsic activity compared with full mu agonist, it can precipitate withdrawal in opioid-dependent animals and humans. These studies suggested that heroin- or methadone-dependent patients may experience opioid withdrawal when they initially receive buprenorphine, thus potentially hindering induction onto clinically effective maintenance doses. Therefore, prior to administering the initial buprenorphine dose, consideration should be given to three important factors. These factors include:

1. The time since last opioid use. The likelihood of buprenorphine-induced precipitated withdrawal increases as the time interval since last opioid use decreases. Because mild withdrawal has been observed at a time interval of 2 hours since last opioid use, the administration of the initial dose of buprenorphine in patients dependent on opioid should be delayed for at least 4 hours after the last ingestion of opioid.

2. The type of opioid dependence (i.e. long or short-acting opioid). Patients dependent on shorter-acting opioid (heroin, morphine) may be less likely to experience buprenorphine-induced precipitated withdrawal than those dependent on long-acting opioid (methadone). A longer time interval between methadone and subsequent buprenorphine dosing is recommended depending on the dose of methadone. For low dose of methadone, the initial dose of buprenorphine can begin at 24 hours after the last ingestion of methadone. For higher doses of methadone, the initiation of buprenorphine can be delayed for more than 24 hours after the last ingestion of methadone.

3. The degree of opioid dependence. The buprenorphine-induced precipitated withdrawal could occur if the degree of opioid dependence is high. For example, patients dependent on >40 mg daily of methadone should reduce their use to 40 mg daily or less of methadone before the first dose of buprenorphine is initiated.

Buprenorphine maintenance therapy

Initial dose of buprenorphine

In most studies, the starting dose of buprenorphine administration on the first
day has been 2 mg of sublingual solution. However, 4 mg of buprenorphine can be administered without causing an opioid withdrawal in opioid-dependent patients. If there is concern for possible precipitation of an opioid withdrawal, the first daily dose can be split with the second half administered 3-4 hours after the first dose. Induction onto a dose as high as 16 mg of buprenorphine has been accomplished by administering 2, 4, 8, and 16 mg of buprenorphine on day 1-4, respectively. However, the objective of induction should be to achieve a maintenance dose (i.e. 16 mg) as quick as possible (i.e. within 2-3 days).

Maintenance dose of buprenorphine

For most patients, an initial target dose should be 12-16 mg of daily buprenorphine. If illicit opioid use or withdrawal continues, then the dose should be increased. The minimum dose increase possible is increment of 2 mg.

Discontinuing buprenorphine

Abrupt discontinuation of buprenorphine produced a mild to moderate withdrawal. Gradual dose reduction is recommended over rapid dose reduction or abrupt cessation since the former has been shown to provide less self-reported withdrawal, increased retention, and less illicit opioid use.

Less-than-daily use with buprenorphine

Because of buprenorphine's long duration of action, less-than-daily dosing with buprenorphine has been suggested. Less-than-daily dosing would likely improve buprenorphine's clinical acceptability to patients who are receiving their medication through a clinic by reducing the required number of clinic visits. Currently, it would be best to recommend a thrice-weekly schedule (e.g. Monday, Wednesday, and Friday), although additional studies of twice-weekly (e.g. Monday and Thursday) dosing may show this schedule is equally effective and also liked by patients. For patients on daily buprenorphine who are switching to thrice-weekly buprenorphine, doses ingested on medication days should be increased to compensate for the longer time period between doses. Because buprenorphine is a partial agonist, maximum agonist effects are below that expected for a full agonist. Thus, increases in the daily doses are safe and well tolerated by patients.

Summary

Clinical studies provide solid support for the use of buprenorphine in the treatment of opioid dependence and demonstrate an equality in the efficacy of buprenorphine and methadone. This suggests that these two medications can be used in opioid-dependent patients with equal success. However, buprenorphine seems to be a better choice, since, for example, it has better safety profile and more limited physical dependence.

Buprenorphine's partial mu opioid agonist profile is responsible for its high safety profile, decreased abused potential and a low level of physical dependence. Buprenorphine also has the ability to blunt the effects of concurrently administered opioid, either through cross-tolerance or pharmacological antagonism, reducing the risk of illicit drug use. Furthermore, buprenorphine's high receptor affinity and slow dissociation from its receptor helps provide its long duration of action and make less-than-daily dosing possible, which may result in higher acceptability in some patients. However, despite its low abuse potential, buprenorphine can produce mu agonist effects, especially with the parenteral use. The likelihood of parenteral abuse can be reduced by using a sublingually administered combination medication containing buprenorphine and naloxone.

In conclusion, buprenorphine can be an effective, safer alternative for methadone in the treatment of opioid dependence.

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