Buprenorphine:
A Primer for Emergency Physicians

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Abstract:

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The recent approval of office based treatment for opioid addiction and FDA approval of buprenorphine will expand treatment options for opioid addiction. Buprenorphine is classified as a partial μ opioid agonist and a weak kappa antagonist. It has a high affinity for the μ receptor with slow dissociation resulting in a long duration of action and an analgesic potency 25 to 40 times more potent than morphine. At higher doses, its agonist effects plateau and it begins to behave more like an antagonist, limiting the maximal analgesic effect and respiratory depression. This "ceiling effect" confers a high safety profile clinically, a low level of physical dependence, and only mild withdrawal symptoms upon cessation after prolonged administration. It is 60-70% bioavailable sublingually, develops peak serum levels at approximately 90 minutes with a half-life of 4-5 hours. Buprenorphine is very lipophilic and brain tissues levels far exceed serum levels. Suboxone contains a mixture of buprenorphine and naloxone. The naloxone is poorly absorbed sublingually and is designed to discourage intravenous use. Subutex, buprenorphine only, will also be available primarily as an initial test dose.

Clinicians will be using this drug for detoxification or for maintenance of opioid addiction. Patients with recent illicit opioid use may develop a mild precipitated withdrawal syndrome with the induction of buprenorphine. Patients on buprenorphine therapy who develop acute pain will require larger than usual doses of opioid agonists to achieve pain control. There is little experience with buprenorphine overdose management. Acute buprenorphine intoxication may present with some diffuse mild

mental status changes, mild to minimal respiratory depression, small but not pinpoint pupils, and relatively normal vital signs. Naloxone either in standard or higher doses may improve the respiratory depression but will have limited effect on other symptoms. Patients with significant symptoms related to buprenorphine should be admitted to the hospital for observation because symptoms will persist for 12 to 24 hours.

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Introduction

The combination of legislation allowing the implementation of office-based treatment for opioid addiction and recent Food and Drug Administration approval of buprenorphine will substantially change the landscape of opioid addiction treatment in the United States. Emergency physicians are not likely to prescribe outpatient buprenorphine but will encounter it as a current medication for a variety of patients. There may also be unintended problems from diversion. It is important to understand the unique pharmacology of buprenorphine in order to develop informed treatment rationales.

Scope of the problem

There are 980,000 long-term users of heroin in the United States and the cost of heroin addiction to the health care system and to society in 1996 was conservatively estimated at $5 billion and $21.9 billion, respectively.[1-3] Only 12-15% of opioid dependent patients are actively enrolled in methadone maintenance.[1,4] Methadone maintenance has been found to be effective in curtailing drug use, reducing crime, enhancing social productivity, and preventing both overdose deaths and the spread of infectious diseases.[5]

Policy

The Drug Addiction Treatment Act of 2000, expands the venues for the treatment of opioid dependence in the United States from specially licensed methadone facilities to physicians' private offices, where schedule III to schedule V drugs can be prescribed.[6,7 8] The responsibility of methadone administration has historically been jointly shared by the Food and Drug Administration and the Drug Enforcement Administration. This organizational structure has created policies that isolated methadone therapy from the medical mainstream and limited the development of physician expertise and creativity.[9] Opioid substitution treatment will now be monitored by the Substance Abuse and Mental Health Administration and will allow the expansion of treatment to private practice. This creates opportunities to provide comprehensive care for addicted patients with AIDS, hepatitis, or other conditions that are complicated by opioid dependence. It is hoped that private treatment will reduce the stigma associated with the use of opioids and will bring addiction treatment into the mainstream of health care and may become similar to that of other chronically ill patients. In addition, this expansion could have substantial public health benefits by reducing heroin demand.[6] Adverse societal outcomes such as ease of diversion and unknown health care costs are possible.

The Act stipulates that physicians must use medications that have been approved by the Food and Drug Administration for maintenance and detoxification treatment of opioid dependence.[9] The Act also requires that physicians notify the Department of Health and Human Services of their intent to prescribe these drugs for outpatient maintenance or detoxification by applying for a special Drug Enforcement Administration number. Physicians treating opioid dependent patients must have specialized training or experience as well as have appropriate counseling and other

services available.[10] A maximum of 30 patients can be treated per physician group.[1] On October 8, 2002, the U.S. Food and Drug Administration approved buprenorphine, a schedule III partial μ agonist, for the treatment of opioid dependence.[6]

Pharmacology

Buprenorphine, a derivative of thebaine, is classified as a partial μ opioid agonist and a weak kappa antagonist.[11] It has a high affinity for the μ receptor with slow dissociation resulting in a long duration of action. In lower doses, buprenorphine has an analgesic potency 25 to 40 times more potent than similar milligram dosages of morphine.[12] Because it is a partial agonist, its effects plateau at higher doses and it begins to behave more like an antagonist. This antagonist property in higher doses limits the maximal analgesic effect and respiratory depression.[1] This high affinity blockade significantly limits the effect of subsequently administered opioid agonists or antagonists.[1] This "ceiling effect" confers a high safety profile clinically, a low level of physical dependence, and only mild withdrawal symptoms upon cessation after prolonged administration. These qualities all make it advantageous for the treatment of opioid dependence. This "ceiling effect" may limit its usefulness in addicts who require higher doses of methadone.

Buprenorphine is well absorbed sublingually with 60-70% of the bioavailability of intravenous doses.[13] Buprenorphine is less well absorbed orally and is quickly metabolized by the liver. The drug is widely distributed with a peak plasma concentration at approximately 90 minutes with a half-life of 4-5 hours. Buprenorphine is very 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.[11] Buprenorphine is mainly metabolized to inactive conjugated metabolites (80-90%) but norbuprenorphine, a product of N-dealkylation via the cytochrome P-450 3A4 enzyme, has more potent respiratory depressive effects than the parent drug.[14,15] Drugs that interfere with 3A4 such as eythromycin, ketoconozole, and HIV protease inhibitors could decrease the production of norbuprenorphine. Drugs that induce 3A4 such as phenobarbital, carbamazepine, and phenytoin could increase the levels of norbuprenorphine.[16 17] The clinical effects of these interactions is not known.

The sublingual preparation approved in the US, marketed under the brand name Suboxone (Reckitt Benckiser, Berkshire, United Kingdom), will be available in 2 mg and 8 mg tablets combined with naloxone 0.5 mg and 2 mg. Naloxone has no effect sublingually because of poor absorption but precipitates withdrawal symptoms if administered parenterally by an opioid-dependent person, thereby limiting diversion.[11,18,19] The sublingual preparation of buprenorphine alone (Subutex) will also be available and is intended for use in the physician supervised introduction of patients new to the drug. Buprenex, the parenteral form of buprenorphine, has been available and used for pain control for decades.

Clinical Use

Buprenorphine has been successfully used for both opioid detoxification and maintenance. It has a better safety profile than methadone.[20] A variety of dosing regimens are being studied to optimize treatment and are more fully covered in other reviews.[11] A regimen of 8-12 mg sublingual daily has been used for 5-7 days for detoxification from opioids.[21] The slow release of buprenorphine from the μ receptor allows a relatively symptom free withdrawal. Physical dependence to buprenorphine is

considered milder than to methadone or heroin and withdrawal signs and symptoms are limited, making discontinuation less uncomfortable. Maintenance doses of 4-32 mg/day will suppress symptoms of withdrawal and reduce illicit opioid use.[22-26] Dosing can be extended to every 2-3 days

Physicians should be aware of the potential problem of precipitating withdrawal symptoms with the induction of buprenorphine. In a patient with an active heroin or methadone effect, the antagonist effect of buprenorphine will prevail. An initial opioid free period must elapse before the initial dose of buprenorphine without naloxone. The induction of buprenorphine should be done in the presence of a physician.[1]

Pain and Addiction Management Issues

The treatment of acute pain in the emergency department may be significantly affected in those patients on buprenorphine maintenance. Clinical and research evidence suggests that persons maintained on long-acting opioid agonists have a lower sensitivity for a given pain stimulus.[27] In addition, patients maintained on methadone and buprenorphine will require higher doses of other opioids to achieve adequate pain relief in the setting of acute pain. The published clinical experience of treating acute pain in buprenorphine maintained patients is limited. The general principals of acute pain management including intravenous administration of opioid analgesics and repeated and timely assessment of pain, blood pressure, and ventilation should suffice in achieving pain control.

Patients that are expected to require pain control in the near future should stop further doses of their buprenorphine one to two days prior to the scheduled procedure.

Because of the slowly waning effect of buprenorphine over the next 12-24 hours, patient controlled analgesia should be monitored carefully.

Physicians can legally use buprenorphine for the inpatient treatment of opioid addiction without the special DEA number and training. The first dose of the buprenorphine without naloxone preparation should be administered in the range of 4-8 mg sublingually and in the presence of a physician to monitor for signs of precipitated withdrawal.

Oral buprenorphine can be used for acute pain management but has limited advantages over existing preparations. Patients who present after missing a dose of buprenorphine should have milder withdrawal symptoms than would occur with methadone. Each hospital should develop its own internal policies on handling this situation.

Overdose Prevention

Methadone maintenance is the only proven effective method of preventing deaths from heroin overdoses.[28,29] The French began to use office-based buprenorphine treatment in 1996 and have reported significant decreases in both fatal and non-fatal heroin overdoses.[30] A review of all deaths reported to the French Police Central Agency on Overdoses for a 5 year period from 1995-1999, showed a decrease from 565 heroin related deaths in the first year to 143 in the fifth year.[11]

Intentional Abuse/Diversion

The experience in France and New Zealand has demonstrated that there is a significant potential for diversion of buprenorphine to intentional abuse by opioid addicts.[31-34] The clinical effects of intravenous buprenorphine were rated by addicts as

comparable to equipotent doses of morphine and heroin.[12] A large percentage of French buprenorphine patients (33%) reported intravenous use.[35] Diversion was also common in New Zealand, but the addition of naloxone significantly decreased its monetary value and its frequency of diversion.[36] The injection of a 4:1 combination of buprenorphine/ naloxone has been demonstrated to result in acute withdrawal symptoms among heroin addicts.[18,19] It is hoped that this combination will minimize the risk for diversion and intravenous use. There may still be concern of diversion to opioid naïve users.

Overdose Deaths

Even though the use of buprenorphine has a salutary effect on decreasing deaths related to heroin overdose and has a better safety profile than methadone, cases of buprenorphine related overdose deaths have been reported.[20,37-40] Twenty-six buprenorphine related overdose deaths have been reported and almost all have occurred with the combination of benzodiazepines and/or alcohol. Most have involved intravenous use of buprenorphine but one massive oral intoxication death has been described.[38]

Acute Overdose Management

There is little clinical experience with the acute overdose management of buprenorphine but some inferences from clinical studies can be made. The "ceiling effect" on the μ receptor should limit life threatening respiratory depression but it has been reported with both intravenous and sublingual doses.[41-44] The intravenous administration of therapeutic doses of buprenorphine increased the diastolic blood pressure, slightly increased the heart rate, and decreased pupil size for 24 hours. Oral administration results in a peak effect that is delayed several hours and can last 8-10

hours. Intravenous or subcutaneous administration of buprenorphine will demonstrate mild respiratory depression in 15 minutes with a maximum effect at 45 minutes and a duration of 6 hours.[1,12]

Hospital based reported buprenorphine overdoses have demonstrated limited symptoms. Three cases of intravenous medical error (buprenorphine 16 mg and 32 mg) caused only insomnia, vomiting and pressure headache without any respiratory depression.[1] One case of buprenorphine 14-16 mg taken orally with suicidal intent reported minimal symptoms.[45]

A case series of 11 cases of severe buprenorphine intravenous overdose was recently described.[44] The history of buprenorphine use was self described and not laboratory confirmed. These patients were described as having a Glascow Coma Score of 8 or less, miosis, and severe respiratory depression. Naloxone in doses of 0.4 mg-0.8 mg caused a rapid improvement in all of these patients. Over half of these patients had also concomitantly used alcohol and/or benzodiazepines. One significant limitation of this study is that any buprenorphine overdose patient who did not respond to naloxone would not be included.

Some clinical research is somewhat contradictory. In these hospital based studies, the administration of naloxone 2 mg after intoxication with buprenorphine will have no effect on the mild respiratory depression.[46] Higher doses such as 5 or 10 mg of naloxone may have some effect on respiratory depression but little effect on mental status changes. These higher doses will not produce withdrawal symptoms. The role of naloxone and the clinical presentation in this scenario is to be determined by future studies. Buprenorphine will not be detected on most emergency department toxicologic screens but will be

detected on more comprehensive tests. Supportive care and observation should be the major treatment modalities in suspected buprenorphine intoxication. Patients with significant symptoms related to buprenorphine should be admitted to the hospital for observation because symptoms will likely persist for 12-20 hours.

Emergency physicians will soon be encountering patients undergoing detoxification or being maintained on outpatient buprenorphine. Its unique pharmacology offers many practical advantages but some distinct difficulties in the treatment of acute pain and the management of acute intoxications. The United States hopes to repeat the experience of other countries that have implemented office based buprenorphine maintenance and have demonstrated significant decreases in heroin related medical complications.

Author Contributions

KS drafted the manuscript and all revisions. KS takes responsibility for the paper as a whole.

References

1. Raisch DW, Fye CL, Boardman KD, Sather MR. Opioid dependence treatment, including buprenorphine/naloxone. *Ann Pharmacother*. 2002;36:312-21.
2. Merrill JO. Policy progress for physician treatment of opiate addiction. *J Gen Intern Med*. 2002;17:361-8.
3. Mark TL, Woody GE, Juday T, Kleber HD. The economic costs of heroin addiction in the United States. *Drug Alcohol Depend*. 2001;61:195-206.
4. Rounsaville BJ, Kosten TR. Treatment for opioid dependence: quality and access. *Jama*. 2000;283:1337-9.
5. Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. *JAMA*. 1998;280:1936-43.
6. Resnick RB. Food and Drug Administration approval of buprenorphine-naloxone for office treatment of addiction. *Ann Intern Med*. 2003;138:360.
7. Fiellin DA, O'Connor PG. Clinical practice. Office-based treatment of opioid-dependent patients. *N Engl J Med*. 2002;347:817-23.
8. Jaffe JH, O'Keeffe C. From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States. *Drug Alcohol Depend*. 2003;70:S3-S11.
9. Fiellin DA, O'Connor PG. New federal initiatives to enhance the medical treatment of opioid dependence. *Ann Intern Med*. 2002;137:688-92.
10. Buprenorphine training from SAMSHA http://buprenorphine.samhsa.gov/ Accessed October 30, 2003.
11. Ling W, Smith D. Buprenorphine: blending practice and research. *J Subst Abuse Treat*. 2002;23:87-92.
12. Pickworth WB, Johnson RE, Holicky BA, Cone EJ. Subjective and physiologic effects of intravenous buprenorphine in humans. *Clin Pharmacol Ther*. 1993;53:570-6.
13. Mendelson J, Upton RA, Everhart ET, Jacob P, 3rd, Jones RT. Bioavailability of sublingual buprenorphine. *J Clin Pharmacol*. 1997;37:31-7.
14. Ohtani M, Kotaki H, Nishitateno K, Sawada Y, Iga T. Kinetics of respiratory depression in rats induced by buprenorphine and its metabolite, norbuprenorphine. *J Pharmacol Exp Ther*. 1997;281:428-33.
15. Ohtani M, Kotaki H, Sawada Y, Iga T. Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic-pharmacodynamic modeling. *J Pharmacol Exp Ther*. 1995;272:505-10.
16. Bridge TP, Fudala PJ, Herbert S, Leiderman DB. Safety and health policy considerations related to the use of buprenorphine/naloxone as an office-based treatment for opiate dependence. *Drug Alcohol Depend*. 2003;70:S79-85.
17. Chiang CN, Hawks RL. Pharmacokinetics of the combination tablet of buprenorphine and naloxone. *Drug Alcohol Depend*. 2003;70:S39-47.

18. Mendelson J, Jones RT, Fernandez I, Welm S, Melby AK, Baggott MJ. Buprenorphine and naloxone interactions in opiate-dependent volunteers. *Clin Pharmacol Ther*. 1996;60:105-14.
19. Mendelson J, Jones RT, Welm S, Baggott M, Fernandez I, Melby AK, Nath RP. Buprenorphine and naloxone combinations: the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. *Psychopharmacology (Berl)*. 1999;141:37-46.
20. Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs buprenorphine in France. *JAMA*. 2001;285:45.
21. Lintzeris N, Bell J, Bammer G, Jolley DJ, Rushworth L. A randomized controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal. *Addiction*. 2002;97:1395-404.
22. Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug Alcohol Depend*. 1995;40:17-25.
23. Ling W, Charuvastra C, Collins JF, Batki S, Brown LS, Jr., Kintaudi P, Wesson DR, McNicholas L, Tusel DJ, Malkerneker U, Renner JA, Jr., Santos E, Casadonte P, Fye C, Stine S, Wang RI, Segal D. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction*. 1998;93:475-86.
24. O'Connor PG, Oliveto AH, Shi JM, Triffleman EG, Carroll KM, Kosten TR, Rounsaville BJ, Pakes JA, Schottenfeld RS. A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. *Am J Med*. 1998;105:100-5.
25. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med*. 2000;343:1290-7.
26. Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, Collins J, Raisch D, Casadonte P, Goldsmith RJ, Ling W, Malkerneker U, McNicholas L, Renner J, Stine S, Tusel D. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *N Engl J Med*. 2003;349:949-58.
27. Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. *Drug Alcohol Depend*. 2001;63:139-46.
28. Sporer KA. Strategies for preventing heroin overdose. *BMJ*. 2003;326:442-4.
29. Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG. Methadone maintenance and addicts' risk of fatal heroin overdose. *Subst Use Misuse*. 1996;31:177-96.
30. Gueye PN, Megarbane B, Borron SW, Adnet F, Galliot-Guilley M, Ricordel I, Tourneau J, Goldgran-Toledano D, Baud FJ. Trends in opiate and opioid poisonings in addicts in north-east Paris and suburbs, 1995-99. *Addiction*. 2002;97:1295-304.
31. Harper I. Temgesic abuse. *N Z Med J*. 1983;96:777.
32. Rainey HB. Abuse of buprenorphine. *N Z Med J*. 1986;99:72.

33. Tacke U. Abuse of buprenorphine by intravenous injection--the French connection. *Addiction*. 2002;97:1355.
34. Quigley AJ, Bredemeyer DE, Seow SS. A case of buprenorphine abuse. *Med J Aust*. 1984;140:425-6.
35. Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti JP. Injecting misuse of buprenorphine among French drug users. *Addiction*. 2001;96:267-72.
36. Robinson GM, Dukes PD, Robinson BJ, Cooke RR, Mahoney GN. The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. *Drug Alcohol Depend*. 1993;33:81-6.
37. Tracqui A, Kintz P, Ludes B. Buprenorphine-related deaths among drug addicts in France: a report on 20 fatalities. *J Anal Toxicol*. 1998;22:430-4.
38. Reynaud M, Petit G, Potard D, Courty P. Six deaths linked to concomitant use of buprenorphine and benzodiazepines. *Addiction*. 1998;93:1385-92.
39. Reynaud M, Tracqui A, Petit G, Potard D, Courty P. Six deaths linked to misuse of buprenorphine-benzodiazepine combinations. *Am J Psychiatry*. 1998;155:448-9.
40. Gaulier JM, Marquet P, Lacassie E, Dupuy JL, Lachatre G. Fatal intoxication following self-administration of a massive dose of buprenorphine. *J Forensic Sci*. 2000;45:226-8.
41. Thorn SE, Rawal N, Wennhager M. Prolonged respiratory depression caused by sublingual buprenorphine. *Lancet*. 1988;1:179-80.
42. Downing JW, Goodwin NM, Hicks J. The respiratory depressive effects of intravenous buprenorphine in patients in an intensive care unit. *S Afr Med J*. 1979;55:1023-7.
43. Schmidt JF, Chraemmer-Jorgensen B, Pedersen JE, Risbo A. Postoperative pain relief with naloxone. Severe respiratory depression and pain after high dose buprenorphine. *Anaesthesia*. 1985;40:583-6.
44. Boyd J, Randell T, Luurila H, Kuisma M. Serious overdoses involving buprenorphine in Helsinki. *Acta Anaesthesiol Scand*. 2003;47:1031-3.
45. Banks CD. Overdosage of buprenorphine: case report. *N Z Med J*. 1979;89:255-7.
46. Gal TJ. Naloxone reversal of buprenorphine-induced respiratory depression. *Clin Pharmacol Ther*. 1989;45:66-71.