REVIEW ARTICLE

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Buprenorphine
Clinical Pharmacokinetics in the Treatment of Opioid Dependence

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Contents

Abstract

Buprenorphine is a semi-synthetic opioid derived from thebaine, a naturally occurring alkaloid of the opium poppy, *Papaver somniferum*. The pharmacology of buprenorphine is unique in that it is a partial agonist at the opioid μ receptor. Buprenorphine undergoes extensive first-pass metabolism and therefore has very low oral bioavailability; however, its bioavailability sublingually is extensive enough to make this a feasible route of administration for the treatment of opioid dependence. The mean time to maximum plasma concentration following sublingual administration is variable, ranging from 40 minutes to 3.5 hours. Buprenorphine has a large volume of distribution and is highly protein bound (96%). It is extensively metabolised by *N*-dealkylation to norbuprenorphine primarily through cytochrome P450 (CYP) 3A4. The terminal elimination half-life of buprenorphine is long and there is considerable variation in reported values (mean values ranging from 3 to 44 hours). Most of a dose of buprenorphine is eliminated in the faeces, with approximately 10–30% excreted in urine. Naloxone has been added to a sublingual formulation of buprenorphine to reduce the abuse liability of the product. The presence of naloxone does not appear to influence the pharmacokinetics of buprenorphine. Buprenorphine crosses the placenta during pregnan-

cy and also crosses into breast milk. Buprenorphine dosage does not need to be significantly adjusted in patients with renal impairment; however, since CYP3A activity may be decreased in patients with severe chronic liver disease, it is possible that the metabolism of buprenorphine will be altered in these patients. Although there is limited evidence in the literature to date, drugs that are known to inhibit or induce CYP3A4 have the potential to diminish or enhance buprenorphine *N*-dealkylation. It appears that the interaction between buprenorphine and benzodiazepines is more likely to be a pharmacodynamic (additive or synergistic) than a pharmacokinetic interaction. The relationship between buprenorphine plasma concentration and response in the treatment of opioid dependence has not been well studied.

The pharmacokinetic and pharmacodynamic properties of buprenorphine allow it to be a feasible option for substitution therapy in the treatment of opioid dependence.

Buprenorphine is a semi-synthetic opioid derived from thebaine, a naturally occurring alkaloid of the opium poppy, *Papaver somniferum*. Buprenorphine is used clinically as an analgesic and as substitution therapy for opioid dependence. This review focuses on the pharmacokinetics of buprenorphine as they relate to its use in the treatment of opioid dependence.

Both opioid receptor agonists (e.g. methadone and levacetylmethadol [LAAM; levo-α-acetylmethadol]) and antagonists (e.g. naltrexone) have been used in the treatment of opioid dependence. The pharmacology of buprenorphine is unique in that it is a partial agonist at the opioid μ receptor.[1,2] Its opioid μ receptor agonist properties produce clinical effects similar to methadone, including analgesia, sedation, euphoria and respiratory depression. However, as a partial agonist, buprenorphine has maximal opioid effects lower than those of full agonists, providing a wider safety margin.[3] For example, in France, where buprenorphine has been available for several years, a retrospective evaluation of sudden deaths that were attributed to the misuse of buprenorphine or methadone estimated a 3-fold higher yearly death rate associated with methadone than with buprenorphine despite the fewer restrictions on buprenorphine prescribing.[4] A potential contributing factor to the increased safety profile of buprenorphine compared with methadone and LAAM could be the apparent lower risk of QT interval prolongation and cardiac toxicity.[5]

Buprenorphine has a long receptor fixation half-life of 40 minutes (compared with milliseconds for morphine),[2] which probably contributes to its prolonged duration of action. This allows for the effective use of less than daily dose administration,[6,7] similar to LAAM or naltrexone but unlike methadone. As a partial opioid receptor agonist with a long duration of action, buprenorphine may also have the advantage of being associated with a delayed and less severe withdrawal syndrome compared with other opioids.[8,9]

Several studies have demonstrated the efficacy of sublingually administered buprenorphine as substitution therapy in the treatment of opioid dependence.[7,10-15] Initial clinical trials used a sublingual alcohol (ethanol) solution of buprenorphine, whereas subsequent trials have used a sublingual tablet that is now available on the market in several countries. A disadvantage buprenorphine shares with other opioid receptor agonists is a potential for abuse. To reduce this risk, buprenorphine is also marketed as a combination sublingual tablet containing both buprenorphine and naloxone in a ratio of 4 : 1. The rationale is that when taken as intended, appreciable amounts of naloxone are not absorbed; however, if the tablets are crushed and injected, naloxone will exert its opioid receptor antagonist properties. There is some experimental research support for this rationale: opioid-dependent individuals using the combination product sublingually did not exhibit withdrawal symptoms;[16,17] buprenorphine and naloxone administered in combination

parenterally to non-physically dependent individuals attenuated (but did not block) the subjective effects of buprenorphine;[18,19] and the combination administered parenterally to physically dependent opioid users precipitated withdrawal symptoms.[17,20-24] The fact that naloxone did not completely block buprenorphine subjective effects[16,17] is probably explained by the relatively high affinity of buprenorphine for the opioid μ receptor. The other important clinical implication is that in the case of buprenorphine overdose, naloxone may not be effective at reversing respiratory depression.[25]

1. Buprenorphine Pharmacokinetics

One challenge in the study of buprenorphine pharmacokinetics has been in the availability of appropriate assays to quantify buprenorphine concentrations. Buprenorphine is 25–40 times more potent than morphine;[26] therefore, acute doses and resulting buprenorphine plasma concentrations are very low, often falling below 1 ng/mL. A radioimmunoassay (RIA) was used in the earlier pharmacokinetic studies;[27] however, it has been shown that this assay may be incapable of distinguishing between buprenorphine and its metabolite, norbuprenorphine.[28] When this was all that was available, it was accepted for use in single-dose studies, since metabolite contributions in this setting may be less than with multiple-dose studies. Newer assays involving mass spectrometry or tandem mass spectrometry, usually coupled to a gas chromatograph or liquid chromatograph, are very specific and are capable of quantifying very low plasma levels (<1.0 ng/mL).[29-31] Therefore, buprenorphine pharmacokinetics have been studied with different assaying techniques over the years, which is likely to have contributed to the variable results obtained and reported in this review.

1.1 Absorption

Buprenorphine undergoes extensive first-pass metabolism and therefore has very low oral bioavailability.[2] Absorption of buprenorphine transdermally is also limited,[32] although a new transdermal matrix patch has been developed for use in patients with pain.[33] The bioavailability of buprenorphine sublingually is extensive enough to make this a feasible route of administration for the treatment of opioid dependence. Studies utilising specific assays have reported buprenorphine sublingual solution's mean bioavailability of 28–51% (table I).[34,35] The plasma bioavailability of the sublingual tablet has been estimated as 49–63% that of the sublingual solution (table I).[36,37] However, the clinical significance of these differences in bioavailability may be limited, based on recent investigations that reported similar opioid-receptor binding changes in subjects (n = 3) taking buprenorphine sublingual liquid (2 and 16mg) compared with subjects (n = 5) taking buprenorphine sublingual tablets (2 and 16mg).[38,39]

A number of factors could possibly influence sublingual absorption and bioavailability. At physiological pH, opioids can exist in ionised and non-ionised forms. By increasing the pH of the oral environment, more of the drug would be in the non-ionised form, therefore potentially enhancing absorption. In a study of the sublingual absorption of selected opioids, it was found that methadone absorption increased from 34% at a saliva pH of 6.5 to 75% at pH 8.5. A similar test could not be done with buprenorphine because of the difficulty of dissolving it in basic pH.[47] One study found a significant but low correlation, suggesting that as saliva pH increased, the recovery of buprenorphine in saliva decreased ($r = -0.33$; $p = 0.05$), indicating increased absorption.[35] In contrast, in another study the same group found no significant correlation between saliva pH and buprenorphine area under the plasma concentration-time curve (AUC) [$r = 0.33$; $p = 0.52$].[36] Likewise, the length of time the dose is held under the tongue seems to have minimal effect on the absorption of buprenorphine, as demonstrated by the bioequivalence of 3- and 5-minute sublingual solution holds,[35] and the similar absorbed fractions after 2.5- and 10-minute sublingual solution holds, under controlled study conditions.[47] It is not known if this is the case for the sublingual tablets. Of course, very short hold times would be likely to reduce the amount absorbed, which may be of concern in some patients who are unwilling to wait for complete tablet dissolution.

Although this demonstrates that buprenorphine is rapidly absorbed into the oral mucosa, absorption into the systemic circulation is slower. The mean

Table I. Summary of studies determining pharmacokinetic parameters of buprenorphine[a]

Study	Subjects	Route	Dosing conditions	F (%)	t_{max} (h)	C_{max} (ng/mL)	V_{ss} (L)	CL (mL/min)	$t_{½\beta}$ (h)	Assay
Kuhlman et al.[34]	Non-dependent heroin users	Buccal	4mg, single dose, plastic strip; buccal hold for 10 min	27.8 ± 8.9 SEM [4.1–42.7][b] n = 4	0.81 ± 0.17 SEM [0.33–1.50] NBUP: 1.29 ± 0.19 SEM [0.75–2.00] n = 4	1.98 ± 0.55 SEM [0.25–3.90] NBUP: 0.50 ± 0.20 SEM [0.03–1.26] n = 6	V_d/F: 5598 ± 990 [3489–9224] n = 5	CL/F: 11 865 ± 7508 [2190–41 400] n = 5	19.01 ± 8.44 SEM [1.32–48.63] NBUP: 73.63 ± 23.72 SEM [13.42–143.1] PST: 96h n = 5	NCI-MS/MS
	Non-dependent heroin users	SL	4mg, single solution dose SL hold for 10 min	51.4 ± 13.2 SEM [12.8–92.9][b] n = 5	0.71 ± 0.08 SEM [0.50–1.00] NBUP: 3.63 ± 0.98 [0.75–7.00] n = 5	3.31 ± 0.81 SEM [1.93–7.20] NBUP: 0.41 ± 0.08 [0.16–0.64] n = 6	V_d/F: 6750 ± 1212 [3203–10376] n = 5	CL/F: 3507 ± 857 [1875–7217] n = 6	27.72 ± 6.08 SEM [5.21–49.09] NBUP: 83.0 ± 33.2 SEM [9.7–216.3] PST: 96h n = 6	NCI-MS/MS
	Non-dependent heroin users	IV	1.2mg, single IV infusion dose (over 1 min)	NA	NA	NA	334.9 ± 116.2 [124.6–770.8] n = 5	1280 ± 218 [960–1922]; n = 5	3.21 ± 1.25 [1.62–8.18] PST: 96h n = 5	NCI-MS/MS
Bullingham et al.[40]	Postoperative	SL	0.4mg, single tablet dose given 3h after a 0.3mg IV dose	55.7 ± 6.0 SEM [43.6–77.8][c] n = 5	3.5 ± 0.67 SEM [2–6][c] n = 5	0.43 ± 0.06 SEM[c] n = 5	NA	NA	NA	RIA
	Postoperative	SL	0.8mg, single tablet dose given 3h after a 0.3mg IV dose	54.1 ± 12.7 SEM [15.7–94.4][c] n = 5	3.2 ± 0.82 SEM [1.5–6][c] n = 5	0.85 ± 0.32 SEM[c] n = 5	NA	NA	NA	RIA
	Operative/ postoperative	IV	0.3mg, single IV dose intraoperatively	NA	NA	NA	NA	NA	5.18 ± 0.55 SEM [3.88–6.39][d] PST: 13h n = 5	RIA
Mendelson et al.[35]	Healthy volunteer	SL	2mg, single solution dose SL hold for 3 min	28 ± 10 [28–36][e] n = 6	NA	1.60 ± 0.66 n = 6	NA	NA	NA	GC-ECD
	Healthy volunteer	SL	2mg, single solution dose SL hold for 5 min	29 ± 10 [29–33][e] n = 6	NA	1.72 ± 0.87 n = 6	NA	NA	NA	GC-ECD
	Healthy volunteer	IV	1mg, single IV infusion dose (over 30 min)	NA	NA	NA	NA	1041 ± 363 n = 6	16.2 ± 20.1[f] PST: 24h n = 6	GC-ECD

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Table I. Contd

Study	Subjects	Route	Dosing conditions	F (%)	t_{max} (h)	C_{max} (ng/mL)	V_{ss} (L)	CL (mL/min)	$t_{½β}$ (h)	Assay
Bullingham et al.[41]	Postoperative	SL	0.4mg, single tablet dose given 3h after a 0.3mg IV dose	31[g] n = 10	NA	NA	NA	NA	NA	RIA
Harris et al.[16]	Opioid-dependent	SL	8mg, solution dose after stabilisation (at least 7 days) on buprenorphine 8mg	~40[h] n = 9	1.00 ± 0.31 NBUP: 1.91 ± 1.13 n = 9	9.40 ± 4.13 NBUP: 2.49 ± 1.06 n = 9	NA	NA	19.8 ± 8.2 PST: 24h n = 9	LC-MS/MS
	Opioid-dependent	SL	8mg, solution dose in combination with naloxone 4mg, after stabilisation (at least 7 days) on buprenorphine 8mg	~40[h] n = 9	1.47 ± 0.48 NBUP: 3.29 ± 2.67 n = 9	8.32 ± 3.74 NBUP: 2.33 ± 1.08 n = 9	NA	NA	23.2 ± 9.3 PST: 24h n = 9	LC-MS/MS
	Opioid-dependent	SL	8mg, solution dose in combination with naloxone 8mg, after stabilisation (at least 7 days) on buprenorphine 8mg	~40[h] n = 9	1.45 ± 0.52 NBUP: 5.08 ± 7.20 n = 9	7.76 ± 2.64 NBUP: 2.88 ± 2.25 n = 9	NA	NA	21.8 ± 11.2 PST: 24h n = 9	LC-MS/MS
	Opioid-dependent	IV	4mg, in combination with naloxone 4.0mg	NA	NA	NA	NA	NA	32.1 ± 12.0 NBUP: 34.6 ± 16.4 PST: 144h n = 9	LC-MS/MS
Nath et al.[36]	Non-dependent opioid users	SL	7.7mg solution, single dose SL hold for 5 min	F_{rel}: 49 ± 25% tablet to solution[i] n = 6	1.2 ± 0.3 n = 6	7.1 ± 2.8 n = 6	NA	NA	NA	Capillary GC-ECD
	Non-dependent opioid users	SL	8mg, single tablet dose SL hold for 5 min	F_{rel}: 49 ± 25% tablet to solution[i] n = 6	0.9 ± 0.3 n = 6	2.9 ± 0.5 n = 6	NA	NA	NA	Capillary GC-ECD
Schuh and Johanson[37]	Opioid-dependent	SL	2mg, solution dose Maintained on dose for at least 7 days SL hold for at least 5 min	F_{rel}: 63% tablet to solution n = 14	2 n = 14	2.04 n = 14	NA	NA	NA	LC-MS/MS

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