ELSEVIER

Drug and Alcohol Dependence 70 (2003) S39–S47

DRUG and ALCOHOL DEPENDENCE

www.elsevier.com/locate/drugalcdep

Review

Pharmacokinetics of the combination tablet of buprenorphine and naloxone

C. Nora Chiang*, Richard L. Hawks

Division of Treatment Research and Development, National Institute on Drug Abuse, 6001 Executive Blvd, Room 4123 Bethesda, MD 20892, USA

Received 19 December 2002; accepted 4 February 2003

Abstract

The sublingual combination tablet formulation of buprenorphine and naloxone at a fixed dose ratio of 4:1 has been shown to be as effective as the tablet formulation containing only buprenorphine in treating opiate addiction. The addition of naloxone does not affect the efficacy of buprenorphine for two reasons: (1) naloxone is poorly absorbed sublingually relative to buprenorphine and (2) the half-life for buprenorphine is much longer than for naloxone (32 vs. 1 h for naloxone). The sublingual absorption of buprenorphine is rapid and the peak plasma concentration occurs 1 h after dosing. The plasma levels for naloxone are much lower and decline much more rapidly than those for buprenorphine. Increasing dose results in increasing plasma levels of buprenorphine, although this increase is not directly dose-proportional. There is a large inter-subject variability in plasma buprenorphine levels. Due to the large individual variability in opiate dependence level and the large variability in the pharmacokinetics (PK) of buprenorphine, the effective dose or effective plasma concentration is also quite variable. Doses must be titrated to a clinically effective level for individual patients.
Published by Elsevier Science Ireland Ltd.

Keywords: Buprenorphine; Naloxone; Pharmacokinetics; Metabolism; Opiate

1. Introduction

A combination tablet containing buprenorphine and naloxone at a fixed dose ratio of 4:1 (2 mg buprenorphine:0.5 mg naloxone and 8 mg buprenorphine:2 mg naloxone) has been approved by the Food and Drug Administration (FDA) for treating opiate dependence. The daily recommended dose of the combination tablet of buprenorphine and naloxone will probably range from 4:1 to 24:6 mg depending on the individual patient's dependence level (Johnson et al., this volume). Buprenorphine, a long acting mu-opiate partial agonist (Jasinski et al., 1978) has been shown to be effective for treating opiate-dependence (Johnson et al., 1992; Fudala and Johnson, 1995; Bickel and Amass, 1995; Ling et al., 1998). Naloxone is a short-acting opiate antagonist and can precipitate a moderate to severe withdrawal syndrome in opiate-dependent individuals (Jasinski et al., 1978; O'Brien et al., 1978). The addition of naloxone to the buprenorphine tablet is intended to reduce the abuse potential of buprenorphine. When buprenorphine and naloxone at a 4:1 ratio were given intravenously to opiate-dependent individuals, the combination dose precipitated opiate-withdrawal signs and symptoms (Fudala et al., 1998; Mendelson et al., 1999). Taken sublingually, the addition of naloxone does not affect the efficacy or pharmacological effects of buprenorphine (Walsh and Eissenberg, 2003; Harris et al., 2000) because of the differential in both sublingual absorption (40% for buprenorphine vs. 10% for naloxone for the solution formulation) (Harris et al., 2000) and duration of action (1 day for buprenorphine vs. 1 h for naloxone) (Jasinski et al., 1978; Berkowitz, 1976). Because of its anticipated limited abuse potential, this combination formulation is expected to be useful in a broad treatment setting that includes office-based practice (Bridge et al., 2003).

This report summarizes the pharmacokinetics (PK) and metabolism data for buprenorphine and naloxone focusing specifically on the combination tablet. Data for

* Corresponding author. Tel.: +1-301-443-5280; fax: +1-301-443-2599.
E-mail address: nchiang@nih.gov (C.N. Chiang).

a buprenorphine solution formulation (typically containing 30% ethanol) will also be presented since it was the formulation used in earlier clinical trials, which provided the basic efficacy data for the buprenorphine alone product. These data in turn provided a significant portion of the data supporting the safety and efficacy of the combination product.

2. Analytical methods

Immunoassay was the method used in most PK studies for buprenorphine in the 1980s (Moore, 1995). The antisera used in these assays typically cross-reacted with one of buprenorphine's primary metabolites, either norbuprenorphine or the glucuronide conjugate of buprenorphine, the extent of which depended on the hapten used to generate the antisera. However, most of the PK studies conducted at the doses relevant for treating opiate addiction were performed in the 1990s. By this time, more specific assay methods had been developed using electron-capture gas chromatography, gas chromatography–mass spectrometry, high pressure-liquid chromatography with electron capture, liquid chromatography–mass spectrometry, or liquid chromatography-tandem mass spectrometry. The limit of quantitation (LOQ) for these methods was generally in the range of 0.05–0.2 ng/ml (Kuhlman et al., 1996; Moody et al., 1997; Everhart et al., 1997; Harris et al., 2000).

3. Buprenorphine

3.1. Absorption and distribution

Buprenorphine is a very lipophilic compound, which readily permeates the gastrointestinal and oral mucosal membrane. However, the oral bioavailability of buprenorphine is very poor (Walter and Inturrisi, 1995) because of a significant first-pass effect. Sublingual administration provides a way to avoid first pass metabolism, but low availability may still occur if part of the dose is swallowed rather than kept under the tongue. The sublingual uptake of buprenorphine is rapid—generally complete in 2–4 min when administered in solution (Weinberg et al., 1988; Abreu and Bigelow, 1996; Mendelson et al., 1997). Increasing the sublingual holding time for the solution to 10 min does not appear to significantly increase the amount absorbed (Weinberg et al., 1988; Mendelson et al., 1997). When given in tablet form, the sublingual uptake is also affected by the dissolution rate of the tablet in saliva. The bioavailability data for buprenorphine in both solution and tablet forms will be presented in detail later.

Studies in rats indicate that buprenorphine is rapidly distributed to the brain and achieves a concentration higher than in the plasma (Ohtani et al., 1995). The red blood cell to plasma ratio of buprenorphine is reported to be close to unity (Bullingham et al., 1980). Buprenorphine is highly bound (96%) to plasma proteins in humans, primarily to α- and β-globulin fractions (Walter and Inturrisi, 1995).

3.2. Metabolism and excretion

Buprenorphine is extensively metabolized by glucuronidation and *N*-dealkylation to form its conjugate and norbuprenorphine, respectively (Fig. 1). Norbuprenorphine further conjugates with glucuronic acid. Cytochrome P450 (CYP) 3A4 is the primary metabolizing enzyme for N-dealkylation (Iribarne et al., 1997; Kobayashi et al., 1998). Extensive metabolism in the gastrointestinal tract and liver, results in low bioavailability of buprenorphine after oral administration. The majority (50–70%) of the dose is excreted in the feces and only 10–30% is excreted in the urine following parenteral or oral administration (Walter and Inturrisi, 1995; Jones and Mendelson, 1997). Only 1.0 and 2.7% of the dose in the urine was excreted as unchanged buprenorphine and norbuprenorphine, respectively. In contrast, more than half of the dose was excreted in the feces in the unconjugated forms of buprenorphine (5% conjugated vs. 33% unconjugated) and norbuprenorphine (2% conjugated vs. 21% unconjugated) (Jones and Mendelson, 1997). A similar metabolite excretion profile was also observed for the subcutaneous, sublingual and oral dosing (Cone et al., 1984)—the conjugated forms of buprenorphine and norbuprenorphine were the major species in the urine while the un-conjugated forms were the major ones in feces. The unconjugated buprenorphine and norbuprenorphine observed in the feces are likely coming from the conjugated metabolites, which are excreted into the bile and subsequently hydrolyzed in the gastrointestinal tract.

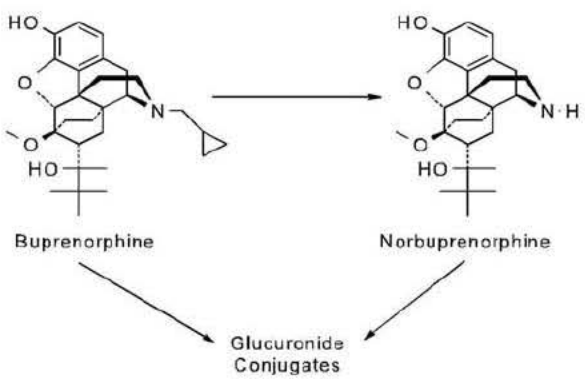

Fig. 1. Metabolic pathways for buprenorphine.

It is likely that enterohepatic recycling of buprenorphine occurs in humans and may contribute to the long terminal half-life and the long duration of action for buprenorphine.

3.3. Metabolite—norbuprenorphine

Norbuprenorphine is a major metabolite of buprenorphine. Following multiple sublingual doses, the peak norbuprenorphine plasma level is lower than that for buprenorphine although trough levels for norbuprenorphine are about 40% higher than those for the parent (Kuhlman et al., 1996; Harris et al., 2000; Jones and Upton, 1997). The overall systemic exposure for norbuprenorphine, estimated from the area under the plasma concentration–time curve (AUC), is approximately equal to that for buprenorphine. However, the brain exposure to norbuprenorphine is expected to be much lower than that for buprenorphine because norbuprenorphine is very polar and does not cross the blood brain barrier as readily as buprenorphine. As evidenced in a study in rats, the brain exposure to norbuprenorphine is less than one-tenth of that for buprenorphine (Ohtani et al., 1997). Since norbuprenorphine is a weak opiate agonist and its intrinsic activity is about one-fourth that of buprenorphine (Ohtani et al., 1995), it can be assumed that norbuprenorphine does not contribute significantly to the efficacy of buprenorphine. A recent study in rats suggests that norbuprenorphine is a more potent respiratory depressant than buprenorphine and that its action may be mediated by the opioid receptors in the lung rather than in the brain (Ohtani et al., 1997). If this holds in humans, norbuprenorphine may contribute to the respiratory depressant effect of buprenorphine.

4. Naloxone

Naloxone is more hydrophilic than buprenorphine. The sublingual absorption of naloxone was significantly lower than that of buprenorphine when determined by either measurement of the unabsorbed drug in the oral rinse (Weinberg et al., 1988) or by classic bioavailability studies (Harris et al., 2000). Naloxone is also rapidly distributed to the brain and has a high brain to plasma ratio (Berkowitz, 1976).

Naloxone is rapidly metabolized by glucuronidation, *N*-dealkylation and reduction of the 6-oxo group to form the conjugated, *N*-dealkylated and the 6-OH metabolites, respectively (Fig. 2). The latter two metabolites are further conjugated with glucuronic acid (Weinstein et al., 1973). The urinary excretion of naloxone is rapid, with 24–37% of a labeled dose appearing in the first 6 h and very little radioactivity measurable after 48 h (Fishman et al., 1973).

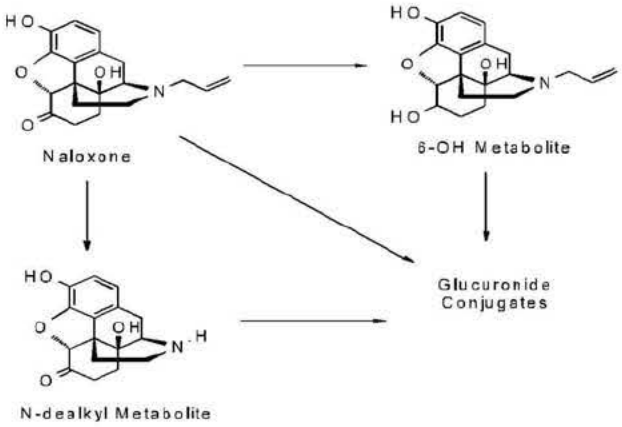

Fig. 2. Metabolic pathways for naloxone.

5. Pharmacokinetics for the intravenous route of administration

In early studies in surgical patients, plasma buprenorphine levels, measured by an immunoassay method, followed a multi-exponential decline after the intravenous administration of 0.3 and 0.6 mg doses of buprenorphine. The half-life was variously reported to be 2–5 h and appeared to depend on when the last plasma sample was taken (Bullingham et al., 1980, 1982; Watson et al., 1982).

A summary of the PK parameters for buprenorphine from recent studies, using more specific assay methods than the earlier studies, is presented in Table 1. In the study by Jones and Upton (1997), an intravenous combined dose of 4 mg buprenorphine and 4 mg naloxone was given to subjects who had been maintained on 8 mg buprenorphine for at least 10 days (the first 7 days with buprenorphine alone followed by buprenorphine 8 mg alone or in combination with 4 mg or 8 mg doses of naloxone). The plasma levels of buprenorphine and naloxone for this study are shown in Fig. 3. The terminal half-life for naloxone was 1.0 h indicating a much more rapid decline than that for buprenorphine, which was characterized by a multi-exponential decline with a mean terminal half-life of approximately 32 h.

When lower doses (1–2 mg) of buprenorphine were used, a shorter mean half-life (3–18 h) was reported although the mean clearances were very close for all the studies, ranging from 59 to 77 l/h (Jones and Upton, 1997; Mendelson et al., 1997; Kuhlman et al., 1996). The large apparent difference in these half-lives may be due to the fact that the plasma levels in these low dose studies declined to the LOQ rapidly and as a result, a terminal half-life could not be reliably estimated. The volume of distribution, a function of half-life, is consequently highly variable—ranging from 335 to 2800 l

Table 1
PK of buprenorphine and naloxone following intravenous administration (mean ± S.D.)

Drug	Dose (mg)	Clearance (l/h)	Half-life (h)	Vd_{ss} (l)	Reference
Buprenorphine	4	58.9 ± 11.5	32.1 ± 12.0	2828 ± 1480	Jones and Upton, 1997
	1	62.5 ± 21.8	16 ± 20	1074 ± 1028	Mendelson et al., 1997
	1.2	76.8 ± 26.2	3.21 ± 2.5	335 ± 232	Kuhlman et al., 1996
Naloxone	4	261 ± 83	1.0 ± 0.43	370 ± 176	Jones and Upton, 1997
	0.4	–	1.1 ± 0.2	–	Nagi et al., 1976

Vd_{ss}, volume of distribution at steady-state.

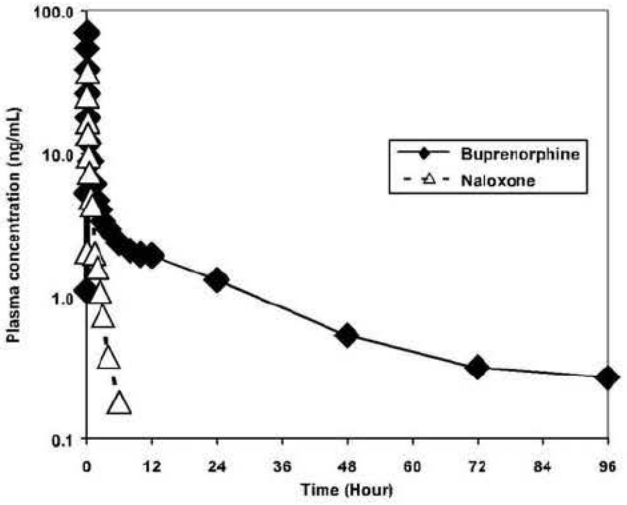

Fig. 3. A semilogarithmic plot of the time course of mean plasma levels of buprenorphine and naloxone following an intravenous administration of a combination of 4 mg buprenorphine and 4 mg naloxone in nine subjects (data from Jones and Upton, 1997).

As presented in Table 1, the half-life for naloxone is 1 h for all the doses (Jones and Upton, 1997; Nagi et al., 1976). The clearance for naloxone is about 260 l/h and the volume of distribution about 370 l.

6. Pharmacokinetics for the sublingual route of administration

6.1. Bioavailability—solution

When administered sublingually in a 30% alcohol solution, the mucosal absorption for buprenorphine was rapid. Absolute bioavailability of approximately 30% was reported for the 2 mg solution dose held under the tongue for either 3 or 5 min (Mendelson et al., 1997). Bioavailability of 51% was reported in a separate study when a 4 mg solution dose was compared with a 1.2 mg intravenous dose (Kuhlman et al., 1996). There was wide variation between subjects in the amount of buprenorphine absorbed in both studies. The maximal plasma concentration for both studies occurred approximately 1 h after dosing and, when corrected for dose, was very close. The difference in bioavailability may be due to the fact that the LOQ of the assay methods used in these two studies were different—0.1 ng/ml for the Mendelson et al. study and 0.2 ng/ml for the Kuhlman et al. study. In the latter study, the plasma levels for most of the subjects declined to LOQ in 13 h after the intravenous dose and resulted in a much shorter apparent terminal half-life of 3 h compared with the terminal half-life of 16 h reported by Mendelson et al. (1997). Consequently, the estimated AUC, for the intravenous dose in the Kuhlman et al. study would be lower and contribute to a higher estimated bioavailability.

The bioavailability of naloxone in sublingual dosing is much lower than that for buprenorphine. In a steady-state study when buprenorphine was given daily for at least 7 days, the absolute bioavailability of sublingual buprenorphine doses of 8 mg, given alone or in combination with 4 and 8 mg of naloxone, was approximately 40% (Harris et al., 2000). The absolute bioavailability of sublingual naloxone, given in combination with 8 mg of buprenorphine, was 9 and 7% for the 4 and 8 mg naloxone doses, respectively (Jones and Upton, 1997 Harris et al., 2000). No significant changes in buprenorphine PK were found with the concurrent administration of naloxone. Table 2 presents a summary of absolute bioavailability data for buprenorphine and naloxone.

6.2. Bioavailability—tablet

The sublingual absorption for the tablet is governed by the saliva dissolution and the partition of the drug through the mucosal membrane into the systematic circulation. The time required for the complete dissolution of the tablets in the saliva is quite variable. In a study by Jones et al. (1997), it took approximately 4 min for the 4:1 mg (two tablets) combination tablet to completely dissolve when held under the tongue and 7 and 8 min, respectively, for the 8:2 mg dose (one tablet) and the 16:4 mg dose (two tablets). There were two incidences with the 8:2 and the 16:4 mg doses, respectively, in which complete dissolution did not occur in 10 min. In general, more time is required for the complete dissolution of higher tablet doses. However, the differ-

Table 2
Sublingual absolute bioavailability for buprenorphine and naloxone (mean ± S.D.)

Drug	Dosage form	Dose (mg)	Dosage regimen	Number of subjects	C_{max} (ng/ml)	T_{max} (h)	Bioavailability (%)	Reference
Buprenorphine	Solution	2	Single dose	6	1.72 ± 0.87	1.62 ± 0.55	30 ± 10	Mendelson et al., 1997
	Solution	4	Single dose	6	3.31 ± 1.81	0.71 ± 0.18	51 ± 29	Kuhlman et al., 1996
	Solution	8	Daily for 7 days	9	9.40 ± 4.13	1.0 ± 0.31	42 ± 9	Jones and Upton, 1997
Naloxone (with 8 mg Buprenorphine)	Solution	4	Daily for 7 days	9	0.66 ± 0.53	0.93 ± 0.25	9 ± 6	Jones and Upton, 1997
	Solution	8	Daily for 7 days	9	0.93 ± 0.71	1.01 ± 0.31	7 ± 4	Jones and Upton, 1997

T_{max}, time to reach maximal plasma concentration after dosing; C_{max}, maximal plasma concentration.

ence in dissolution times did not appear to have any significant effect on the absorption rate of buprenorphine. Buprenorphine is rapidly absorbed and peak concentration occurred at 1 h for all the three doses (4:1, 8:2 and 16:4 mg) when administered sublingually. A typical plasma concentration–time curve following sublingual administration of the combination tablet for the 16:4 mg dose (the dose used for the efficacy trial) is presented in Fig. 4. The maximal concentration for norbuprenorphine, a major metabolite of buprenorphine, occurred at about 1 h and the level was lower than that for buprenorphine. Naloxone levels were much lower than buprenorphine and fell below the detection limit (0.05 ng/ml) in approximately 3 h.

6.3. Relative bioavailability of tablet to solution

There is no apparent difference in the time (T_{max} of 1 h) to reach the peak concentration between the solution formulation and the tablet formulation (Nath et al., 1999). However, the bioavailability for the tablet formulation is lower than that for the solution formulation. There is a very large intersubject variability for the relative bioavailability of the tablet to the solution formulation. The relative bioavailability was reported to be 50% (range of 11–82%) in a single dose study comparing the 8 mg buprenorphine solution to the 8 mg tablet in six subjects (Nath et al., 1999). In a multiple-dose study, 24 subjects received the 8 mg buprenorphine solution for 10 days and the 16 mg buprenorphine tablet dose for 10 days in a randomized crossover design. The relative bioavailability for tablet to solution determined by the steady-state plasma concentration was 71% (range 40–110%) (Ajir et al., 2000).

In another multiple dose study, 14 opiate dependent patients were maintained on daily buprenorphine doses using an ascending order of 2, 4, and 8 mg solution doses followed by an 8 mg tablet dose. Patients were on each dose for at least 7 days. The relative bioavailability of the 8 mg tablet compared with the 8 mg solution was 64% (Schuh and Johanson, 1999). The higher bioavailability observed for the multiple dose study as compared with the single dose study may be due to the fact that the plasma levels used in the estimation of the AUC for the multiple dose study (24 h steady-state plasma levels) were all above the LOQ. In the single dose study, the plasma levels quickly declined to the LOQ making it difficult to reliably estimate the terminal half-life and the extrapolated area under the curve used in the calculation of bioavailability. As a result, the single dose study may underestimate the bioavailability. A difference might also result from the subjects having learned to hold the tablet under the tongue better during the multiple dosing schedule which would in turn result in improved absorption of buprenorphine. The steady-state data probably provides a better estimate of the relative

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.