

Chapter 2

Controlled Drug Administration Studies of High-Dose Buprenorphine in Humans

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1. INTRODUCTION

Buprenorphine was developed in the early 1970s by Reckitt and Colman Products (Hull, UK) as part of a wide-ranging search for an effective analgesic with lower abuse potential and reduced toxicity compared with morphine (1). Many of buprenorphine's chemical and pharmacological properties, including ready diffusion of the highly lipophilic drug across the blood-brain barrier and its high binding avidity for opiate receptors, led to the selection of this thebaine derivative as the best analgesic compound for further drug development. Despite its high-affinity binding and high potency (25–40 times more potent than morphine), buprenorphine has a lower efficacy for pain relief and is classified as a partial agonist at μ opiate receptors. Buprenorphine dissociates slowly from receptors, resulting in a long duration of action and, potentially, a reduced potential for abuse. These properties led researchers at the United States Public Health Service's Addiction Research Center to investigate buprenorphine further as a pharmacotherapy for opioid addiction (2).

Several important factors need to be considered when reviewing the buprenorphine literature. Over the last 25 yr, investigators have studied the agonist and antagonist characteristics of buprenorphine alone and its interactions when coadministered with other opioids. Buprenorphine may substitute for another opioid, suppress response to an opioid, or precipitate withdrawal from an opioid, depending on the dose of buprenorphine administered and conditions at the time of administration. Careful consideration must be given

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to participant drug use history, frequency, magnitude and length of opioid use, buprenorphine dosing regimen, and the nature of studied effects, for all of these parameters can affect the interpretation of research findings. In addition, evaluation of buprenorphine concentration data requires an understanding of the sensitivity and specificity of the analytical method employed. Much of the early buprenorphine literature utilized a highly sensitive but nonspecific radioimmunoassay (RIA) that crossreacted extensively with buprenorphine metabolites. At the time, chromatographic methods could not meet the sensitivity requirements mandated by the low concentrations of buprenorphine and metabolites found in plasma.

This chapter reviews controlled drug administration studies of buprenorphine in humans and focuses primarily on its use as a pharmacotherapeutic agent for opioid dependence, but important findings from analgesic research are included when appropriate. It examines buprenorphine's bioavailability following alternative routes of drug administration, dose effect profiles, abuse liability, and toxicity. The reader is referred to additional discussions on buprenorphine's efficacy as a replacement maintenance medication in opioid addiction treatment and buprenorphine poisonings in medical examiner cases included in later chapters of this book.

2. BIOAVAILABILITY

Intravenous (im) buprenorphine for analgesia was released for the treatment of moderate to severe pain in 1977. The oral route of drug administration was not pursued because substantial first-pass metabolism of buprenorphine led to limited oral bioavailability of approx 15% (3). Extensive hepatic oxidative metabolism of buprenorphine by the cytochrome P450 3A4 isoenzyme was shown to produce the *n*-dealkylated metabolite, norbuprenorphine, a weak μ agonist with limited ability to penetrate the blood-brain barrier (4). Therefore, a sublingual (sl) preparation for use in cancer patients unable to tolerate the oral route because of nausea and vomiting and the parenteral route because of poor venous access, emaciation, or coagulation defects was also made available. The sublingual or buccal route of buprenorphine administration also avoided first-pass metabolism, minimized side effects owing to lower peak drug concentrations (i.e., sedation and constipation), and allowed rapid drug absorption owing to a high lipid to water partition coefficient (5). Disadvantages of the sl route include an unpalatable taste, mucosal irritation, and large intersubject variability.

Early pharmacokinetic studies by Bullingham et al. (6) observed maximum plasma concentrations ($C_{\max}$) approx 3 h after sl administration of 0.4

and 0.8 mg of buprenorphine with an absorption half-life of 76 min. A good dose-concentration relationship was noted at these low doses, and sl bioavailability was found to be approximately 55% based on the nonspecific RIA (7). Weinberg et al. (8) reported rapid absorption of sl buprenorphine into the oral mucosa, but a slower absorption from this tissue reservoir of drug into the systemic circulation. Buprenorphine absorption via the sl route at these low doses was found to be dose independent with maximal absorption into the oral mucosa by 2.5 min. In addition, the duration of action of sl buprenorphine was found to be longer than that found after equianalgesic doses of iv or im preparations, most likely owing to an available reservoir of drug in the oral mucosa. Further evidence for a mucosal reservoir of drug was noted by Cone et al. (9), who reported elevated salivary buprenorphine concentrations for up to 12 h in subjects treated with sl buprenorphine, in contrast to low salivary concentrations following im administration. Equivalent plasma and saliva concentrations of buprenorphine were not realized until 24–48 h after the end of chronic sl dosing.

Buprenorphine is a highly lipophilic compound that accumulates in the tissues to a much higher extent than in blood with chronic dosing (10). This tissue depot contributes to the long terminal elimination half-life (42 h) of the drug and suggested that transdermal delivery of buprenorphine could, perhaps, be a feasible route of drug administration for chronic pain (11). Effective analgesia has been achieved with transdermal buprenorphine, although a lag time of 1–6 h was observed even with an ethanol-based delivery device (12,13). Attempts to deliver drug via the transdermal route in concentrations sufficient for treatment of opioid dependence were unsuccessful (14).

The long half-life of buprenorphine and strong binding to opiate receptors led Fudala et al. (15) to evaluate the effectiveness of alternate-day administration of buprenorphine in the treatment of opioid addiction. Although subjects had a significantly greater urge for opioids on days when they did not receive buprenorphine, they were able to tolerate 48 h between doses. In addition, only mild to moderate opioid withdrawal symptoms developed following abrupt termination of drug after chronic treatment. Peak effects on the Himmelsbach withdrawal scale occurred after 3–5 d of abstinence and lasted for up to 10 d. These data indicate that the combined factors of an extended plasma half-life for buprenorphine and accumulated drug stored in the tissues following chronic dosing provide sufficient drug concentration to allow alternate-day drug administration and to delay the onset of severe withdrawal symptoms.

Tablet sl formulations offer advantages over liquid ones including increased drug stability, ease of storage, simplified drug administration, and

reduced potential for accidental ingestion by children. Mendelson et al. (16,17) evaluated absorption of sl buprenorphine from tablets containing 4–32 mg of drug alone and in combination with naloxone. The mean buprenorphine area under the curve (AUC) and $C_{\max}$ were found to increase with increasing dose, but dose-corrected AUC was lower for each increase in dose. These findings are in disagreement with those found with the liquid sl preparation, indicating a possible difference in absorption between the liquid and tablet sl formulations. A ceiling on sl buprenorphine absorption may occur with the tablet formulation and may contribute to observed ceiling effects on buprenorphine opioid agonist effects when tablets are administered. Later studies determined bioavailability of buprenorphine from the sl tablet to be approx 50% that of the liquid sl formulation (18,19).

3. DOSE-EFFECT PROFILES

Buprenorphine has a bell-shaped dose-response curve. Early studies demonstrated a lack of orderly dose effect responses for pain relief after 0.2–0.8 mg of sl buprenorphine (20), for euphoria following 0.2–2 mg of subcutaneous (sc) buprenorphine (2), and for respiratory depression following 0.3 and 0.6 mg of iv buprenorphine (3,21). Because studies documenting the success of buprenorphine in reducing heroin use and increasing retention of patients in opioid treatment programs also suggested that higher doses of sl buprenorphine could improve treatment outcomes (22–24), Walsh et al. (25) studied the safety, tolerability, and abuse liability of up to 32 mg of sl buprenorphine in opioid-experienced but nondependent volunteers. Subjective effects and respiratory depression failed to increase in a dose proportional manner with higher sl buprenorphine doses. Maximal effects were always reached prior to the highest 32-mg dose. Despite increases in plasma buprenorphine concentrations with higher sl doses, behavioral and physiological responses did not increase, documenting that the observed ceiling effect was not owing to limited sl absorption. Another important observation from this study was the increased duration of action noted after high sl doses. Euphoria and miosis lasted up to 3 d after a single acute 32-mg sl dose of buprenorphine. The investigators suggested that the lower efficacy of buprenorphine at higher doses could reduce the risk of overdose and perhaps its abuse liability, increasing the safety of buprenorphine maintenance therapy.

4. ABUSE LIABILITY

Heroin, morphine, and other semisynthetic opioids produce μ -agonist reinforcing effects sometimes leading to self-administration and physical

dependence owing to their high potential for abuse liability. Treatment of iv heroin dependence reduces the health and social consequences of drug addiction, the transmission of infectious diseases including the human immunodeficiency virus (HIV), and drug-related criminal activity. Pharmacotherapy for opiate addiction, especially in conjunction with behavioral treatment, reduces drug use. Methadone, levomethadyl acetate, and naltrexone are approved opioid agonist and antagonist treatments for opioid addiction in the United States. Opioid agonist replacement medications are currently only available from a few highly regulated treatment programs. Patients are required to receive daily or alternate-day medications under observed conditions except when they have demonstrated significant progress in their treatment and earned the privilege of occasional "take-home" doses. This stringent control on medications is needed to prevent drug diversion and iv self-administration. The search continues for additional useful medications with low abuse potential that would allow patients to obtain needed treatment more readily.

Buprenorphine is one of the most promising new analgesics. A partial agonist at μ opiate receptors, buprenorphine can antagonize the euphoria produced by other opiates. It also has a long duration of action and decreased physical dependence following chronic treatment. However, buprenorphine does produce morphine-like subjective feelings, increasing the potential for drug diversion and abuse.

Jasinski et al. (2) first suggested that buprenorphine be used as a maintenance drug for opioid dependence. Buprenorphine's abuse potential was found to be limited with less euphoria at higher sc doses. Furthermore, its long half-life prevented the onset of withdrawal until 14 d after the last dose of buprenorphine following 30–57 daily doses of 8 mg subcutaneously. Withdrawal symptoms were found to be mild and lasted only a few days. These characteristics suggested that daily or less frequent dosing could be effective in buprenorphine treatment of addicts. A substantial potential for abuse of buprenorphine by the iv route was noted in a study assessing the subjective effects of 0.3, 0.6, and 1.2 mg of iv buprenorphine in nondependent opiate users (26). Intravenous buprenorphine produced positive responses on reliable predictors of abuse liability including "feel drug" questionnaires and increased drug "liking," "good effects," and euphoria scores (as measured by the morphine benzedrine [MBG] scale of the Addiction Research Center Inventory [ARCI]).

One of the important factors in selecting a therapeutic medication for opiate dependence is the drug's acceptability to patients. Naltrexone is an effective opioid antagonist and useful in the treatment of addiction, but it is disliked by many opiate abusers and compliance to treatment has been poor (27,28). Buprenorphine produces increases in positive subjective effects, albeit

at a lower magnitude than full μ agonists. Up to 4 mg of sl buprenorphine and up to 2 mg of sc buprenorphine were observed to produce varying degrees of euphoria with increased subject-reported drug-liking scores (29). Study participants identified the drug as opiate-like and reported little dysphoria and sedation. Administration of sl buprenorphine was shown to delay the onset of reinforcing effects as compared to iv administration, reducing its abuse potential. An sl drug delivery system was recommended for treatment of opioid dependence to reduce illicit drug diversion (compared to injectable drug), to reduce manufacturing cost (compared to oral preparations that have more limited bioavailability), and to facilitate drug administration as compared to the sc route.

Illicit use of buprenorphine by the iv route may become especially problematic when heroin cost is high and its supply unreliable (30–32). A creative approach to the problem of potential diversion of therapeutic buprenorphine has been the addition of naloxone, a μ opiate antagonist, to the medication. An im combination of 0.3 mg of buprenorphine and 0.2 mg of naloxone provided good analgesic relief, similar to buprenorphine alone, with only a slightly delayed time of onset. The bioavailability of sl naloxone was estimated to be approx 30%, thus providing some antagonism to buprenorphine's effects at this low agonist:antagonist ratio. Plasma concentrations of naloxone after the oral route are close to zero owing to extensive first-pass metabolism (8).

Preston et al. (34) evaluated physiological and behavioral effects of buprenorphine and naloxone alone and in different combinations in opioid-dependent humans. Subcutaneous buprenorphine alone (0.2 and 0.3 mg) produced no significant effects on any measure, whereas sc naloxone alone (0.2 mg) precipitated abstinence. The sc combinations of 0.2 mg of buprenorphine and 0.2 mg of naloxone, and sc 0.3 mg of buprenorphine and 0.2 mg of naloxone sc also produced an attenuated withdrawal, suggesting a lower abuse potential for the combination product.

Combinations of im buprenorphine and naloxone were also tested in non-dependent opioid abusers (35). Buprenorphine alone produced dose-related opioid agonist effects on physiological and subjective measures. When administered with similar concentrations of naloxone (0.4 mg/70 kg of buprenorphine and 0.5 mg/70 kg of naloxone), opioid agonist effects were attenuated; higher ratios of naloxone:buprenorphine resulted in complete attenuation of opioid effects. The combination product was recommended as a means of lowering the abuse liability of buprenorphine alone, similar to the reduction in abuse of pentazocine-naloxone tablets. In another study in eight opiate-experienced volunteers, naloxone, in a 1:4 ratio with buprenorphine, did not alter sl

buprenorphine pharmacokinetics or pharmacodynamic effects and did not produce opioid withdrawal (16).

5. TOXICITY

Opiates, such as morphine and heroin, produce respiratory depression in a dose-related manner. Although parenteral buprenorphine also was shown to decrease responsiveness to increasing plasma carbon dioxide concentrations, this effect was much less than that seen following morphine (36). Further support for the high therapeutic index of buprenorphine was found in the lack of clinically relevant respiratory effects in individuals receiving up to 16 mg/d of sl buprenorphine for 84 d while participating in an opioid replacement research protocol (37). The maximum observed decrease in respiratory rate was two breaths per minute at the highest dose of buprenorphine.

In 1979, in one of the first reported buprenorphine overdose cases, it was noted that ingestion of approx forty 0.4-mg buprenorphine tablets by the sl or oral route (the route could not be definitively identified) produced minimal drowsiness and no respiratory or hemodynamic disturbances (38). The partial agonist action of buprenorphine and reduced bioavailability by the oral and sl routes may account for this limited toxicity (39,40). In a study of nondependent healthy individuals (41), respiratory rate and oxygen saturation were found to be minimally affected following 8 mg of sl buprenorphine. Furthermore, up to 7 mg of parenteral buprenorphine produced no clinically significant respiratory depression in 50 female cesarian section patients who received the drug for analgesia (42). In fact, respiratory depression was rarely found to be significant, except when used together with other depressants, especially benzodiazepines, during surgery (43–46).

Zanette et al. (47) report a serious case of buprenorphine interaction involving an 11-yr-old female who developed severe and prolonged respiratory depression following administration of 4 µg/kg of im buprenorphine 12 h after surgery for relief of pain and restlessness. Her respiration had been stable after a successful surgical procedure that utilized diazepam, fentanyl, and other drugs for anesthesia. However, while in the intensive care unit, an additional 10 mg of diazepam was administered, reinstituting full respiratory insufficiency. The authors of this report warn of the dangers of coadministration of multiple sedative drugs. Respiratory and cardiovascular collapse has been reported in patients receiving therapeutic doses of buprenorphine and diazepam (48). Reports from France, where high-dose buprenorphine has been available since 1996 for opioid maintenance treatment, indicate that physicians may be putting patients

at risk by not following suggested dosing recommendations and continuing to coprescribe buprenorphine and benzodiazepines (49).

The interaction between buprenorphine and benzodiazepines may be the result of pharmacokinetic or pharmacodynamics effects. In an *in vitro* investigation of the interaction of buprenorphine and benzodiazepines with Cyp3A enzymes from rat and human microsomes, Ibrahim et al. (50) found that the observed enzyme inhibition at typical plasma concentrations of benzodiazepine was unlikely to be responsible for excessive central nervous system (CNS) depression. An additive or synergistic pharmacological effect, unrelated to the pharmacokinetic interaction, was suggested as the cause of decreased respiratory function.

Interactions between the antidepressant amitriptyline and buprenorphine have also been reported; antidepressants may be commonly coprescribed with analgesics especially when chronic pain is accompanied by depression (51). Sublingual buprenorphine alone depressed respiration, but a significant increase in end-tidal carbon dioxide was noted 2–4 h after coadministration of amitriptyline and buprenorphine. Concurrent administration of selective serotonin reuptake inhibitor antidepressants (e.g., fluvoxamine) has also been shown to increase the bioavailability of buprenorphine owing to noncompetitive inhibition of the P450 3A4 isoenzyme (52). HIV-1 protease inhibitors, ritonavir and indinavir, also competitively inhibit *n*-dealkylation of buprenorphine (53). Cyp 3A4 represents about 30% of the total P450 content of the human liver; many licit and illicit drugs are known to induce or inhibit these enzymes and, hence, buprenorphine metabolism. Thus, the observed toxicity of buprenorphine and other medications may be the result of complex pharmacokinetic and pharmacodynamic interactions.

High concentrations of norbuprenorphine may also contribute to buprenorphine toxicity. Utilizing extracted and unextracted samples and two different RIA antisera, Hand et al. (54) were able to estimate buprenorphine and metabolite concentrations after chronic dosing. Plasma concentrations of norbuprenorphine were low after single doses of buprenorphine, but equivalent to parent drug concentrations after daily dosing. Two- to threefold higher concentrations of buprenorphine glucuronide, the primary product of phase II metabolism, were found with chronic dosing. Although norbuprenorphine is much less potent than buprenorphine in producing analgesia, Ohrani et al. (55) have recently reported its higher respiratory depressant potency (10 times that of the parent drug). Increased plasma concentrations of norbuprenorphine may therefore, contribute to buprenorphine toxicity, although its ability to enter the brain is limited. Ohtani et al. (55) suggest that norbuprenorphine binding to μ receptors in the lung could account for its respiratory effects or

that multiple μ receptor subtypes associated with analgesia or respiratory depression could bind with different affinities to buprenorphine and norbuprenorphine.

More than 70% of a buprenorphine dose is eliminated in the feces; renal clearance is much less important for drug clearance. Therefore, administration of buprenorphine may be advantageous over other analgesics when renal insufficiency is present. However, increased concentrations of the metabolites, free and conjugated norbuprenorphine and buprenorphine glucuronide, can increase dramatically when renal function is reduced. Poor renal function could lead to higher norbuprenorphine concentrations, increasing the potential for respiratory depression.

6. SAFETY AND ABUSE LIABILITY OF HIGH-DOSE INTRAVENOUS BUPRENORPHINE

Concerns have been raised about the potential diversion and iv abuse of buprenorphine once it is approved for use in the United States. The safety and abuse liability of iv buprenorphine in the range of doses recommended for maintenance treatment have not been evaluated. In addition, although ceilings on physiological and subjective effects have been shown with high sl doses of buprenorphine, this phenomenon has not been tested at high iv doses. We (Clinical Pharmacology and Therapeutics Research Branch, NIDA) designed a protocol to determine the acute health risks of sl opioid maintenance doses if abused by the iv route, to evaluate the abuse liability of iv buprenorphine in nondependent iv opioid users, to characterize the effects of dose and time on behavior following high-dose iv buprenorphine, and to characterize the pharmacokinetics of buprenorphine and norbuprenorphine after iv administration (56–59).

Sublingual buprenorphine (placebo or 12 mg) was held under the tongue for 5 min followed by iv buprenorphine administration of (placebo or 2, 4, 8, 12, or 16 mg) to six healthy male nondependent opioid users in this preliminary dose-escalation study. Physiological measures, including blood pressure (BP), heart rate, transcutaneous oxygen saturation, respiration rate, and skin temperature, were monitored continuously for 3 h and intermittently for 72 h after dosing. Visual analog scales for “any drug effects,” “drug liking,” “good effects,” “bad effects,” “high,” “feel sick,” and “desire opiates,” an adjective rating scale; and a shortened form of the ARCI monitored subjective drug effects over the same time frame.

Intravenous administration of up to 16 mg of buprenorphine was shown to be safe in experienced, nondependent opioid abusers. It must be stressed

that toxicity was minimal at these doses of buprenorphine alone. Combinations of buprenorphine and other compounds with respiratory depressant action have shown considerable toxicity. Various degrees of sedation, nausea, vomiting and itching were observed in participants in this study. Subjects were easily aroused with voice prompts and completed computer questionnaires and tasks throughout the experimental session. Some individuals became irritable after receiving these high iv doses of buprenorphine, but no other mental status changes were observed. One individual experienced severe nausea and vomiting after the 12-mg iv dose and did not participate in the highest 16-mg iv dose.

No significant differences from placebo in BP, heart rate, respiration rate, oxygen saturation, or skin temperature across time and drug conditions were noted (56). The only statistically significant difference was an increase in the 3-h AUC for systolic BP after the 8-mg iv dose (+13.5 mmHg). The mean ($\pm$ SD) maximum decrease in oxygen saturation from baseline was -7.3% (± 4.3) and was highest for the 8-mg iv dose.

All active buprenorphine conditions produced increases in positive subjective measures compared to placebo, including high, drug effect, good effects, drug liking, opioid agonist adjective rating scale, and MBG scale of the ARCI (56). Mean change from baseline scores ($n = 5$) for drug high as measured by Visual Analog Scale are shown for placebo, and for 2, 4, 8, 12, and 16 mg of iv buprenorphine in Fig. 1. Data are shown for the first 3 h after administration of drug. It is apparent that the strongest high effects were obtained following the 12-mg iv dose. Large interindividual differences in the magnitude of subjective effects were observed. Peak effects occurred 1–1.5 h after iv doses and 3–6 h after sl buprenorphine with a duration of action of 24–72 h. Effects did not increase in an orderly dose-related manner. On many measures, the magnitude of effect was not different between all active doses, consistent with a ceiling effect and partial agonist activity for buprenorphine. The effects of 16 mg intravenously tended to be less than those of 12 mg and varied in comparison with other active doses. The effects of 12 mg sublingually were similar in magnitude to 4, 8, and 12 mg intravenously. The abuse potential of iv buprenorphine does not appear to increase with dose, nor does there appear to be a substantial difference in abuse potential between iv and sl buprenorphine at the doses tested.

Increases in subjective and physiological measures were not dose related and supported the presence of a ceiling effect for these parameters following iv administration. Plasma concentrations of buprenorphine and norbuprenorphine were also determined for up to 72 h after drug administration by liquid chromatography-tandem mass spectrometry. The limits of quantitation for buprenorphine and norbuprenorphine were 0.1 ng/mL utilizing deuterated

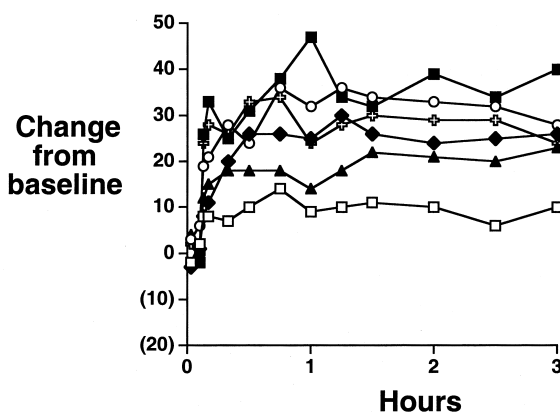


Fig. 1. Time course of mean change from baseline for drug high as measured with a Visual Analog Scale questionnaire ($n = 5$) following iv buprenorphine. Placebo (□), 2 (◆), 4 (○), 8 (▲), 12 (■), or 16 mg (⊕) iv buprenorphine was injected by a physician in a constant volume of 4 mL over 60 s to nondependent, opiate-experienced volunteers. Mean data for five of the six subjects are included because one subject in the trial did not receive the highest 16-mg in dose of buprenorphine.

internal standards for both analytes. Peak plasma concentrations of buprenorphine and norbuprenorphine occurred 0.5–2 h and 0.5–12 h after sl administration of drug. Peak plasma concentrations increased in an orderly dose-related manner suggesting that observed ceiling effects were owing to pharmacodynamic rather than pharmacokinetic factors. Doses were administered intravenously, ensuring that drug absorption was not a limiting factor.

Bioavailability following the sl route was determined to be approx 35%, in close agreement with another estimate obtained with a highly specific chromatographic method (57). This is in contrast to earlier bioavailability estimates for sl buprenorphine of 55–65% that were based on nonspecific RIA measurements (7).

7. CONCLUSION

Buprenorphine, a partial μ agonist and k antagonist, which is 25–40 times more potent than morphine, is an effective analgesic and opioid maintenance treatment for heroin addiction. Standard im analgesic doses are 0.3 mg. Significantly higher doses of sl buprenorphine (up to 24 mg) are necessary to reduce heroin abuse and improve patient retention in opioid addiction treatment. Higher sl doses are used because of the lower bioavailability (approx

35%) of this route of drug administration. Flattened or inverted U-shaped dose-response curves have been demonstrated for physiological and subjective effects of up to 32 mg of sl and up to 16 mg of iv buprenorphine. Even by the iv route, buprenorphine appears to have a ceiling for cardiorespiratory effects and to have a high therapeutic index. It must be cautioned that buprenorphine alone was administered under carefully supervised medical conditions in these studies and that the effects of buprenorphine in combination with other CNS sedatives may produce considerable toxicity. Buprenorphine produces positive subjective responses, indicating a potential for abuse, but the abuse potential does not appear to increase with increasing doses of buprenorphine. The use of a combined buprenorphine-naloxone sl formulation may further reduce its abuse potential.

REFERENCES

1. Lewis JW, Readhead MJ. Novel analgesics and molecular rearrangements in the morphine-thebaine group. XVIII. 3-deoxy-6,14-endo-etheno-6,7,8,14-tetrahydro-orphavines. *J Med Chem* 1970;13:525-7.
2. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine. *Arch. Gen. Psychiatry* 1978;35:501-16.
3. McQuay HJ, Moore RA, Bullingham RES. Buprenorphine kinetics. In: *Advances in pain research and therapy*, Foley KM, Inturrisi CE eds., New York: Raven, 1986.
4. Iribarne C, Picart D, Dreano Y, Bail JP, Berthou F. Involvement of cytochrome P450 3A4 in n-dealkylation of buprenorphine in human liver microsomes. *Life Sci* 1997;60(22):1953-64.
5. Payne R. Novel routes of opioid administration: part 1-sublingual and buccal. *Primary Care Cancer* 1989; January:55-6.
6. Bullingham RES, Dwyer D, Allen MC, Moore RA, McQuay HJ. Sublingual buprenorphine used postoperatively: clinical observations and preliminary pharmacokinetic analysis. *Br J Clin Pharmacol* 1981;12:117-22.
7. Bullingham RES, McQuay HJ, Porter EJB, Allen MC, Moore RA. Sublingual buprenorphine used postoperatively: ten hour plasma drug concentration analysis. *Br J Clin Pharmacol* 1982;13:665-73.
8. Weinberg DS, Inturrisi CE, Reidenberg B, Moulin DE, Nip TJ, Wallenstein S, Houde RW, Foley KM. Sublingual absorption of selected opioid analgesics. *Clin Pharmacol Ther* 1988;44:335-42.
9. Cone EJ, Dickerson SL, Darwin WD, Fudala P, Johnson RE. Elevated drug saliva levels suggest a "depot-like" effect in subjects treated with sublingual buprenorphine. *NIDA Res Monogr* 1991;105:569.
10. Walter DS, Inturrisi CE. Absorption, distribution, metabolism, and excretion of buprenorphine in animals and humans. In: *Buprenorphine: combatting drug abuse with a unique opioid*, Cowan A, Lewis JW, eds., New York: Wiley-Liss, 1995.
11. Kuhlman JJ, Levine B, Johnson RE, Fudala PJ, Cone EJ. Relationship of plasma buprenorphine and norbuprenorphine to withdrawal symptoms during dose induc-

- tion, maintenance and withdrawal from sublingual buprenorphine. *Addiction* 1998;93(4):549–59.
12. Cowan A, Doxey JC, Harry EJ. The animal pharmacology of buprenorphine, an oripavine analgesic agent. *Br J Pharmac* 1977;60:547–54.
13. Wilding IR, Davis SS, Rimoy GH, Rubin P, Kurihara-Bergstrom T, Tipnis V, Berner B, Nightingale J. Pharmacokinetic evaluation of transdermal buprenorphine in man. *Intl J Pharmac* 1996;132:81–7.
14. Stinchcomb AL, Paliwal A, Dua R, Imoto H, Woodard RW, Flynn GL. Permeation of buprenorphine and its 3-alkyl-ester prodrugs through human skin. *Pharm Res* 1996;13:1519–23.
15. Fudala PJ, Jaffe JH, Dax EM, Johnson RE. Use of buprenorphine in the treatment of opioid addiction. II. Physiologic and behavioral effects of daily and alternate-day administration and abrupt withdrawal. *Clin Pharmacol Ther* 1990;47:525–34.
16. Mendelson J, Jones RT, Upton R, and Lin E. Dose-proportionality of sublingual buprenorphine and naloxone tablets. *Clin Pharmacol Ther* 1998;63(2):204.
17. Mendelson J, Upton R, Lin E, Welm S, Jones RT. Dose proportionality of 4, 8, 16 and 32 mg sublingual buprenorphine solutions. *Am Soc Clin Pharmacol Ther* 1999;154.
18. Nath RP, Upton RA, Everhart T, Cheung P, Shwonek P, Jones RT, Mendelson JE. Buprenorphine pharmacokinetics: relative bioavailability of sublingual tablet and liquid formulations. *J Clin Pharmacol* 1999;39:619–23.
19. Mendelson J, Upton R, Jones RT, Jacob P III. Buprenorphine pharmacokinetics: bioequivalence of an 8 mg sublingual tablet formulation. *College on Problems of Drug Dependence*, Scottsdale, AZ 1998.
20. Wallenstein SL, Kaiko RF, Rogers AG, Houde RW. Clinical analgesic assay of sublingual buprenorphine and intramuscular morphine. In: NIDA research monograph, Harris, L ed. Rockville, MD: NIDA Research Monograph, 1982.
21. de Klerk G, Matti, H, Spierdijk J. Comparative study on the circulatory and respiratory effects of buprenorphine and methadone. *Acta Anaesthesiol Belgica* 1981; 32:131–9.
22. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA* 1992;267:2750–55.
23. Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone maintenance for opioid dependence. *J Nerv Ment Dis* 1993;181(6):358–64.
24. Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry* 1996;53:401–7.
25. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther* 1994; 55:569–80.
26. Pickworth WB, Johnson RE, Holicky BA, Cone EJ. Subjective and physiologic effects of intravenous buprenorphine in humans. *Clin Pharmacol Ther* 1993; 53:570–6.
27. Mello NK, Mendelson JH. Buprenorphine treatment of cocaine and heroin abuse. In: *Buprenorphine: combatting drug abuse with a unique opioid*. Cowan A, Lewis JW eds. New York: Wiley-Liss, 1995.

28. Preston KL, Silverman K, Umbricht A, DeJesus A, Montoya ID, Schuster CR. Improvement in naltrexone treatment compliance with contingency management. *Drug Alcohol Depend* 1999;54:127–35.
29. Jasinski DR, Fudala PJ, Johnson RE. Sublingual versus subcutaneous buprenorphine in opiate abusers. *Clin Pharmacol Ther* 1989;45:513–9.
30. Quigley AJ, Bredemeyer DE, Seow SS. A case of buprenorphine abuse. *MJA* 1984;142:425–6.
31. Lewis JW. Buprenorphine. *Drug Alcohol Depend* 1985;14:363–72.
32. Tebbett IR. Analysis of buprenorphine by high-performance liquid chromatography. *J Chromatogr* 1985;347:411–3.
33. Vanacker B, Vandermeersch E, Tomassen J. Comparison of intramuscular buprenorphine and a buprenorphine/naloxone combination in the treatment of post-operative pain. *Curr Med Res Opin* 1986;10:139–44.
34. Preston KL, Bigelow GE, Liebson IA. Buprenorphine and naloxone alone and in combination in opioid-dependent humans. *Psychopharmacology* 1988;94:484–90.
35. Weinhold LL, Preston KL, Farre M, Liebson IA, Bigelow GE. Buprenorphine alone and in combination with naloxone in non-dependent humans. *Drug Alcohol Depend* 1992;30:263–74.
36. Baster TJ, Gibbs JM, Richardson T. Effect of buprenorphine on the ventilatory response to carbon dioxide. *Anaesth Intensive Care* 1977;5:128–33.
37. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther* 1988;247:47–53.
38. Banks CD. Overdosage of buprenorphine: case report. *N Z Med J* 1979;89:255–7.
39. Heel RC, Brogden RN, Speight TM, Avery GS. Buprenorphine: A review of its pharmacological properties and therapeutic efficacy. *Drugs* 1979;17:81–110.
40. McQuay HJ, Bullingham RES, Paterson GMC, Moore RA. Clinical effects of buprenorphine during and after operation. *Br J Anaesth* 1980;52:1013–9.
41. Teoh SK, Mendelson JH, Mello NK, Kuehnle J, Sintavanarong P, Rhoades EM. Acute interactions of buprenorphine with intravenous cocaine and morphine: an investigational new drug phase I safety evaluation. *J Clin Pharmacol* 1993;13:87–99.
42. Budd K. High dose buprenorphine for postoperative analgesia. *Anaesthesia* 1981;36:900–3.
43. Faroqui MH, Cole M, Curran J. Buprenorphine, benzodiazepines and respiratory depression. *Anaesthesia* 1983;38:1002–3.
44. 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.
45. Sekar M, Mimpriss TJ. Buprenorphine, benzodiazepines and prolonged respiratory depression. *Anaesthesia* 1987;42:567–8.
46. 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(1):226–8.
47. Zanette G, Manani G, Giusti F, Pittoni G, Ori C. Respiratory depression following administration of low dose buprenorphine as postoperative analgesic after fentanyl balanced anaesthesia. *Paediatr Anaesth* 1996;6:419–22.

48. Lober C. Buprenorphine. Drug Information Update: Hartford Hosp 1988; 52(5): 285–7.
49. Seyer D, Dif C, Balthazard G, Sciortino V. Traitement de substitution par buprenorphine-haut-dosage: les recommandations sont-elles suivies? *Therapie* 1998;53:349–54.
50. Ibrahim RB, Wilson JG, Thorsby ME, Edwards DJ. Effect of buprenorphine on CYP3A activity in rat and human liver microsomes. *Life Sci* 2000;66:1293–8.
51. Saarialho-Kere U, Mattila MJ, Paloheimo M, Seppala T. Psychomotor, respiratory and neuroendocrinological effects of buprenorphine and amitriptyline in healthy volunteers. *Eur J Clin Pharmacol* 1987;33:139–46.
52. Iribarne C, Picart D, Dreano Y, Berthou F. In vitro interactions between fluoxetine or fluvoxamine and methadone or buprenorphine. *Fundam Clin Pharmacol* 1998;12:194–9.
53. Iribarne C, Bethou F, Carlhant D, Dreano Y, Picart D, Lohezic F, Riche C. Inhibition of methadone and buprenorphine n-dealkylations by three HIV-1 protease inhibitors. *Drug Metab Dispos* 1998;26(3):257–60.
54. Hand CW, Baldwin D, Moore RA, Allen MC, McQuay HJ. Radioimmunoassay of buprenorphine with iodine label: analysis of buprenorphine and metabolites in human plasma. *Ann Clin Biochem* 1986;23:47–53.
55. Ohtani M, Kotaki H, Nishitaten 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.
56. Umbricht A, Huestis MA, Cone EJ, Preston KL. Safety of burprenorphine: ceiling for cardio-respiratory effects at high IV doses. *NIDA Res Monograph* 1998;179:225.
57. Mendelson J, Upton RA, Everhart ET, Jacob P III, Jones RT. Bioavailability of sublingual buprenorphine. *J Clin Pharmacol* 1997;37(1):31–7.

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