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Original Research Article

The Pharmacokinetics and Local Tolerability of a Novel Sublingual Formulation of Buprenorphine

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Abstract

Aim. The principal study objective was to investigate the pharmacokinetic characteristics and determine the absolute bioavailability and tolerability of a new sublingual (SL) buprenorphine wafer.

Methods. The study was of open label, two-way randomized crossover design in 14 fasted healthy male and female volunteers. Each participant, under naltrexone block, received either a single intravenous dose of 300 mcg of buprenorphine as a constant infusion over five minutes or a sublingual dose of 800 mcg of buprenorphine in two treatment periods separated by a seven-day washout period. Blood sampling for plasma drug assay was taken on 16 occasions throughout a 48-hour period (predose and at 10, 20, 30, and 45 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 48 hours postdose). The pharmacokinetic parameters were determined by noncompartmental analyses of the buprenorphine plasma concentration-time profiles. Local tolerability was assessed using modified Likert scales.

Results. The absolute bioavailability of SL buprenorphine was 45.4% (95% confidence interval = 37.8–54.3%). The median times to peak plasma concentration were 10 minutes and 60 minutes after IV and SL administration, respectively. The peak plasma concentration was 2.65 ng/mL and 0.74 ng/mL after IV and SL administration, respectively. The half-lives were 9.1 hours and 11.2 hours after IV and SL administration, respectively. The wafer had very good local tolerability.

Conclusions. This novel sublingual buprenorphine wafer has high bioavailability and reduced Tmax compared with other SL tablet formulations of buprenorphine. The wafer displayed very good local tolerability. The results suggest that this novel buprenorphine wafer may provide enhanced clinical utility in the management of both acute and chronic pain.

Background. Buprenorphine is approved for use in pain management and opioid addiction. Sublingual administration of buprenorphine is a simple and noninvasive route of administration and has been available for many years. Improved sublingual formulations may lead to increased utilization of this useful drug for acute and chronic pain management.

Key Words. Acute Pain; Analgesic; Narcotics; Opioids; Pain Management; Pain Medicine; Safety; Research

Introduction

Buprenorphine has been used clinically for more than 30 years. It is a semisynthetic derivative of the opiate alkaloid thebaine and is approximately 25 to 50 times more potent than morphine in terms of analgesia. A 300-mcg dose of IV buprenorphine is equianalgesic to 10 mg of intravenous (IV) morphine [1–3]. Buprenorphine is a highly lipophilic compound that easily penetrates the mucosa as well as the blood-brain barrier, resulting in rapid brain distribution; however, there is delayed onset of analgesia due to slow receptor association kinetics [4,5]. Brain-to-plasma concentration ratios of buprenorphine in rats following a single

intravenous dose ranged from three at 15 minutes to 10.5 at six hours postadministration [4,5].

Buprenorphine is a potent analgesic acting on the four opioid receptors (agonist on the μ, δ, and opioid receptor–like [ORL-1] receptors and antagonist on the κ-receptor) [6]. Buprenorphine's high affinity for the μ-opioid receptor causes analgesia, respiratory depression, and sedation. It has traditionally been considered a partial μ-opioid receptor agonist based on extrapolation from in vitro and some early animal studies. However, as only about 70% of the μ-receptors are occupied in therapeutic analgesic doses, buprenorphine behaves more as a full μ-opioid receptor agonist for analgesia [4]. Buprenorphine has therefore no ceiling effect for analgesia, but for respiratory depression [7]. This means additional safety, but does not mean that it cannot cause respiratory depression [8], possibly through the metabolites norbuprenorphine and norbuprenorphine-3-glucuronide [6].

It is slow to dissociate off the μ-opioid receptor, resulting in a longer duration of analgesia [9] than most opioids and milder opioid withdrawal symptoms upon termination of chronic treatment [10].

Buprenorphine agonist activity on the ORL-1 also results in analgesic effect and causes less slowing of the peristaltic movement of the gastrointestinal tract, resulting in less constipation [11]. ORL-1 activation is thought to attenuate the dopaminergic reward system (lowering potential for abuse), produce antihyperalgesia, and result in slowing of the development of analgesic tolerance [11–15].

Buprenorphine is also a high-affinity κ-opioid receptor antagonist and a low-affinity δ-opioid receptor antagonist. The κ-opioid receptor antagonist results in less gonadal axis or testosterone depression (opioid-induced androgen depression [OPIAD]), a common side effect seen in most long-term opioid treatments [16–19]. Because it is less likely to supress the gonadal axis and testosterone levels than other opioids, buprenorphine may cause less reduction in sexual desire, mood disturbance, fatigue, and osteoporosis.

Currently, high-dose buprenorphine (without or with naloxone) is widely used as opioid substitution for opioid dependence. However, there is renewed interest in using buprenorphine to treat acute and chronic nociceptive and neuropathic pain due to the benefits described above. When compared with other opioids, buprenorphine does not significantly prolong the corrected Q and T waves in the cardiac electric cycle (QTc) interval [20]. However, labeling requires the warning of the potential for QTc interval prolongation and advises that buprenorphine should not be used in patients with long QT syndrome or a family history thereof or in those taking class 1A or class 3 antiarrhythmic medications. Buprenorphine has reduced effects on the immune and endocrine systems and is associated with less sudden death compared with commonly used opioids and reduced abuse liability [15]. No dose adjustment is required with buprenorphine in renal compromised and elderly patients, especially when used in the short term for analgesia, unlike with other opioids [11,21]. Buprenorphine can be safely used in opioid rotation from conventional opioids, especially low- to moderate-dose opioids with minimal risk of withdrawal or exposure to inadequate analgesia [22,23]. It also provides longer pain relief, six to seven hours compared with four to five hours for morphine [24].

Buprenorphine is currently available nonparenterally in sublingual tablet and transdermal patch formulations. Sublingual (SL) tablets exhibit slow disintegration (6–12 minutes), with a time to peak plasma concentration of two to four hours (Temgesic PI) [25]. Transdermal patches have a slow absorption profile, with detectable levels in the plasma only after 17 hours (Norspan PI) [26]. This has contributed to the limited clinical usefulness of buprenorphine in the management of acute pain.

This study evaluated a novel SL wafer, which was prepared by freeze-drying an aqueous dispersion of buprenorphine hydrochloride (equivalent to 800 mcg of buprenorphine base) containing sodium carboxymethylcellulose and amylopectin as the matrix formers [27]. The buprenorphine wafer dissolves rapidly when placed under the tongue.

The primary aim of this open-label study was to investigate the pharmacokinetic profile of this novel buprenorphine wafer and to establish its absolute bioavailability and local tolerability via the SL route.

Methods

The study was approved by the Bellberry Human Research Ethics Committee (HREC) and was registered with the Australian Therapeutic Goods Administration under the Clinical Trial Notification scheme (CTN 04869–1) and with the Australian and New Zealand Clinical Trials Registry (ACTRN12617000002381). The study was conducted in accordance with the principles of the Declaration of Helsinki [28] and Good Clinical Practice Guidelines [29].

Design

The study was of open-label, two-way, randomized, crossover design in 14 fasted healthy male and female volunteers who all gave written informed consent. Each participant received either a single 300-mcg IV dose as a constant infusion over five minutes or an 800-mcg SL wafer dose of buprenorphine in two treatment periods separated by a seven-day washout period. A seven-day washout period was deemed sufficient as low-dose buprenorphine was reported to exhibit a shorter effective half-life (approximately five hours) than what has been observed with buprenorphine at higher doses [25]. The sequence of the two formulations was according to a computer-generated randomization code.

Clinical

Blood sampling for plasma drug assay and clinical assesment of local tolerability and safety were carried out for 48 hours following both dosing occasions.

Key inclusion criteria were age 18–65 years, BMI of 19–30 kg/m^2 (inclusive), and good general health.

Participants received naltrexone 50 mg per oral (PO) 12-hourly (12 hours and one hour prior to dosing and 12 hours postdosing). Following a 10-hour fast, participants were administered IV buprenorphine or a sublingual buprenorphine wafer followed by a 48-hour pharmacokinetic sampling period postdose. A total of 16 blood samples were collected per volunteer per occasion (predose and at 10, 20, 30, and 45 minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, and 48 hours postdose).

About six mL of whole blood was collected into prechilled K_2EDTA tubes at each time point. Plasma samples were collected as close as possible to the scheduled time point. If it was not possible to collect the sample exactly on the time point, a +/- one-minute window was allowed for the 10-minute through 1.5-hour samples, a +/- two-minute window was allowed for the two-hour through eight-hour samples, and a +/- five-minute window was allowed for the 12-hour through 48-hour samples. Actual times were recorded for all sample draw times. Any deviation outside the specified ranges was clearly documented in the participant's study records.

Immediately after the collection of each sample, the collection tube was gently inverted and then placed in wet ice. Within 60 minutes of withdrawal, the tubes were centrifuged at about 1,900 × gravity (3,400 rpm) for 10 minutes to separate the cells from the plasma. Within 120 minutes of the collection time, the storage tubes were placed into a freezer at approximately –80 °C. They remained in the freezer until analysis.

When participants received the buprenorphine SL wafer, study staff performed a sublingual assessment prior to administering the wafer and postdose at 20 minutes, two hours, and 24 hours. Study staff noted the color of mucosa and whether inflammation was present. To assess the local tolerability profile of the SL formulation, modified Likert scales (0–3; normal to abnormal: 0 = none, 1 = mild, 2 = moderate, 3 = severe) were completed by participants postdose at 20 minutes, two hours, and 24 hours. The following subjective parameters of the wafer formulation were elicited: mucosal irritation, burning sensation, bitterness.

Safety assessments included scheduled adverse event probes, spontaneous adverse event (AE) reporting, physical examination, routine laboratory investigations, electrocardiograms, and vital sign evaluation.

Vital signs (including systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) were performed predose and at 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours postdose. Pulse oximetry was recorded predose and continuously for the first hour postdose.

Laboratory

Safety laboratory testing (biochemistry, hematology, and urinalysis) was performed predose and at 48 hours postdose in each period.

Quantification of the plasma concentrations of buprenorphine and norbuprenorphine was performed using a validated high performance liquid chromatography method with ultraviolet detection, an Low level of quantification (LLOQ) of 0.025 ng/mL for buprenorphine, and an LLOQ of 0.02 ng/mL for norbuprenorphine.

Data Analysis

Standard noncompartmental analysis methods were used to obtain pharmacokinetics variables for buprenorphine and norbuprenorphine for both routes of administration (C_{max} = maximum observed plasma concentration, AUC_{inf} = total area under the plasma concentration time curve extrapolated to time infinity, AUC_{last} = total area under the plasma concentration time curve from the first to the last measurable data point, CL = clearance, T_{max} = time of C_{max}, Vz = apparent volume of distribution, and $t_{1/2}$ = terminal half- life).

The bioavailability after SL dosing was estimated by the ratio of dose-adjusted AUC_{inf} following IV and SL dosing.

Results

Fourteen healthy male and female volunteers with a mean age of 25 years (SD = 7.6 years) and body mass index of 26.1 kg/m^2 (SD = 2.8 kg/m^2) took part in the study. In all but two volunteers, the SL wafer had dissolved within 30–120 seconds. These two volunteers had a complete wafer dissolution time of 10 minutes, although more than 90% of the wafer had disintegrated within five minutes.

The absolute bioavailability after SL dosing, estimated by the ratio of dose-adjusted AUC_{inf} of buprenorphine following IV and SL dosing, was 45.4% (37.8–54.3%), with 26.9% intrasubject variability.

The plasma concentration-time data for buprenorphine are shown graphically in Figure 1, and the pharmacokinetic data are listed in Table 1. Figure 2 and Table 2 show the plasma concentration-time data for norbuprenorphine and the pharmacokinetic data, respectively.

The plasma concentration time curves for SL buprenorphine were higher than for the IV administration from 1.5 hours to 12 hours (Figure 1). The plasma concentration curves were then similar (superimposed on each other) after the 12-hour time point.

However, the plasma concentration time curve for the metabolite norbuprenorphine was

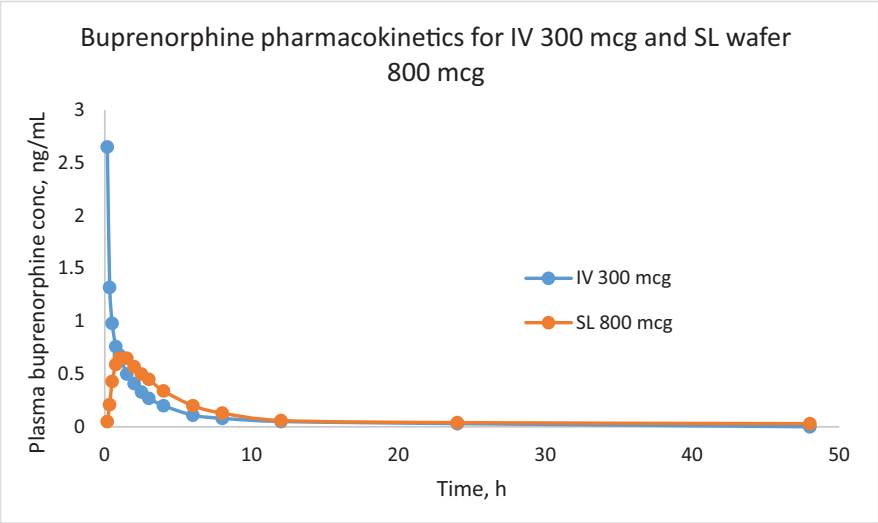

Figure 1 Plasma buprenorphine concentration vs time curve.

Table 1 Individual pharmacokinetics buprenorphine (IV 300 mcg; SL 800 mcg)

Subject No.	Cmax, ng/mL		Tmax, h		AUCtlast, h*ng/mL		AUCinf, h*ng/mL		T1/2, h		CL/F, L/h	
Statistic	IV	SL	IV	SL	IV	SL	IV	SL	IV	SL	IV	SL
R001	1.94	0.47	0.17	2	4.12	2.89	4.61	4.03	9.76	19.4	65.1	198
R002	2.45	1.03	0.17	1.5	3.49	7.97	3.87	8.5	9.11	14.8	77.5	94.1
R003	2.02	1.33	0.18	1	5.04	6.03	5.92	7.01	13.4	26.6	50.7	114
R004	3.41	0.63	0.17	0.75	3.61	3.45	3.96	3.76	6.46	5.47	75.8	212
R005	3.36	0.68	0.17	2	4.04	4.31	4.42	4.66	8.81	6.93	67.8	172
R006	2.23	0.9	0.17	2.02	4.37	6.45	5.02	8.88	11.2	39.3	59.8	90.1
R007	2.08	1.03	0.17	0.75	3.3	4.33	3.45	4.52	3.5	4.32	86.9	177
R008	1.86	0.64	0.17	0.75	2.62	2.05	3.16	2.23	13.8	4.09	95	358
R009	2.84	0.93	0.17	1	2.98	4.8	3.39	5.18	11.1	9.5	88.4	155
R010	2.92	0.41	0.17	0.5	3.64	1.9	4.52	2.84	13.4	19.2	66.3	282
R011	2.2	0.58	0.17	1.5	2.05	4.6	2.41	5.48	6.36	23.4	124	146
R012	3.54	0.76	0.17	3	4.62	6.65	5.26	7.56	11	20.1	57.1	106
R013	3.88	0.53	0.17	0.75	3.73	2.79	4.38	3.23	13.7	6.04	68.4	248
R014	3.52	1.07	0.17	1	2.49	4.55	2.84	4.72	5.32	4.61	105	170
N	14	14	14	14	14	14	14	14	14	14	14	14
Mean	2.73	0.784	0.17	1.32	3.58	4.48	4.09	5.19	9.78	14.5	1,049	3,204
Std dev	0.7	0.269	0	0.71	0.84	1.81	0.98	2.08	3.35	10.6	353	2,016
CV, %	26	34	2.70	54.00	24	40	24	40	34	73	34	63
Median	2.65	0.718	0.17	1	3.63	4.44	4.17	4.69	10.4	12.1	973	2,139
Minimum	1.86	0.412	0.17	0.5	2.05	1.9	2.41	2.23	3.5	4.09	438	1,103
Maximum	3.88	1.33	0.18	3	5.04	7.97	5.92	8.88	13.8	39.3	1,890	7,812
Geomean	2.65	0.741	0.17	1.17	3.48	4.13	3.97	4.81	9.13	11.2	994	2,686
GeoCV, %	26	36	3	55	26	46	25	43	43	90	36	68

AUCtlast = $AUC_{0-48\,hours}$; AUCinf = $AUC_{0-inf\ hours}$; CL/F = clearance/bioavailability.

higher with the SL administration compared with the IV administration from 0.75 hours to 48 hours (Figure 2).

The time to buprenorphine peak plasma concentrations (median T_{max}) following the IV infusion was 10 minutes (the first pharmacokinetics sampling time point), five

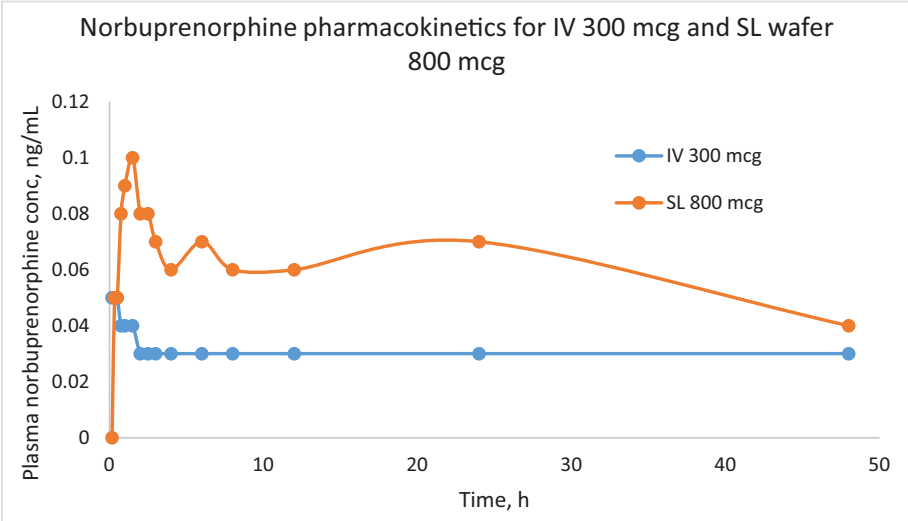

Figure 2 Plasma norbuprenorphine vs time curve.

Table 2 Individual pharmacokinetics norbuprenorphine (IV 300 mcg; SL 800 mcg)

Subject No.	Cmax, ng/mL		Tmax, h		AUCtlast, h*ng/mL		AUCinf, h*ng/mL		T1/2, h		CL/F, L/h	
Statistic	IV	SL	IV	SL	IV	SL	IV	SL	IV	SL	IV	SL
R001	0.06	0.13	2	2	2.06	4.09	NA	NA	NA	NA	NA	NA
R002	0.05	0.06	0.33	24	0.106	2.31	NA	NA	NA	NA	NA	NA
R003	0.06	0.25	1	1.5	0.313	4.46	NA	NA	NA	NA	NA	NA
R004	0.03	0.1	0.33	6	0.238	2.48	NA	NA	NA	NA	NA	NA
R005	0.05	0.07	0.17	12	1.2	2.24	NA	NA	NA	NA	NA	NA
R006	0.03	0.1	0.33	1.5	0.366	3.53	NA	NA	NA	NA	NA	NA
R007	0.08	0.12	0.33	2	0.48	3.32	NA	NA	NA	NA	NA	NA
R008	0.07	0.12	0.33	1.5	0.773	2.34	NA	NA	NA	NA	NA	NA
R009	0.16	0.19	0.17	1	1.56	3.23	NA	NA	NA	NA	NA	NA
R010	0.04	0.13	0.33	0.75	0.026	2.63	NA	NA	NA	NA	NA	NA
R011	0.06	0.06	0.17	6.02	0.115	2.17	NA	NA	NA	NA	NA	NA
R012	0.06	0.09	0.17	1	0.838	3.23	NA	NA	NA	NA	NA	NA
R013	0.07	0.13	0.33	1.5	0.921	3.06	NA	NA	NA	NA	NA	NA
R014	0.07	0.13	0.33	1.5	0.183	3.32	NA	NA	NA	NA	NA	NA
N	14	14	14	14	14	14	0	0	0	0	0	0
Mean	0.063	0.12	0.45	4.45	0.656	3.03						
Std dev	0.032	0.051	0.49	6.43	0.61	0.71						
CV, %	52	43	109.00	145.00	93	23						
Median	0.058	0.122	0.33	1.5	0.423	3.14						
Minimum	0.03	0.057	0.17	0.75	0.026	2.17						
Maximum	0.163	0.252	2	24	2.06	4.46						
Geomean	0.057	0.111	0.34	2.42	0.388	2.96						
GeoCV, %	44	42	79	136	184	23						

AUCtlast = $AUC_{0-48\,hours}$; AUCinf = $AUC_{0-inf\ hours}$; CL/F = clearance/bioavailability.

minutes after the end of the IV infusion. For the sublingual wafer, the median T_{max} occurred approximately 60 minutes after the SL administration.

The time to norbuprenorphine peak plasma concentrations (median T_{max}) following the IV infusion was 20 minutes, 15 minutes after the end of the IV infusion.

For the sublingual wafer, the median T_{max} for norbuprenorphine occurred approximately 1.5 hours after SL administration.

In 43% of participants (6/14) following SL administration, quantifiable buprenorphine plasma concentrations (LLOQ < 0.025 ng/mL) occurred at the first postdose sampling time point at 10 minutes, whereas 93% (13/14) of participants had a quantifiable buprenorphine plasma concentration within 20 minutes.

Only 7% of the participants (1/14) following SL administration had a quantifiable norbuprenorphine plasma concentrations (LLOQ < 0.02 ng/mL) by the second pharmacokinetics sampling time point at 20 minutes, 57% of the participants (8/14) at 30 minutes postdose, 86% of the participants (12/14) at 45 minutes postdose, and 100% of the participants had quantifiable norbuprenorphine plasma concentrations at one hour; 100% of the participants in the IV-administered group had quantifiable norbuprenorphine at the 10-minute pharmacokinetics sampling time point.

The terminal elimination half-lives ($T_{1/2}$) for IV and SL were comparable at 9.1 hours (min–max = 3.5–13.8 hours) and 11.2 hours (min–max = 4.1–13.8 hours; geomean), respectively.

The C_{max} for IV and SL were 2.65 ng/mL and 0.74 ng/mL (geomean), respectively (a 3.6-times higher C_{max} for IV infusion compared with SL administration).

The volume of distribution (Vz) and for IV and SL were 75.5 liters (min–max = 51–124 liters) and 170 liters (min–max = 94–358 liters; geomean), respectively (2.3 times higher Vz for SL compared with IV administration).

The extrapolated portion of the AUC_{INF} for both routes of administration was 24% for IV and 38% for SL dosing.

The AUC_{last} for norbuprenorphine after IV and SL administration were 0.388 h.ng/mL and 2.96 h.ng/mL, respectively or 7.6 times higher for SL administration.

In this study, treatment-emergent adverse effects (TEAEs, Table 3 for complete adverse events) were reported in eleven of fourteen subjects (79%). This included eight of 14 subjects (57%) following dose administration with sublingual buprenorphine wafer 800 mcg and eight of fourteen subjects (57%) following dose administration with IV Buprenorphine 300 mcg, with a total of twenty four treatment-emergent AEs.

There were no deaths or other serious adverse effects (SAEs). No subjects were withdrawn or terminated the study prior to completion. There were no clinically significant abnormailities or clear differences in vital signs and clinical laboratory safety assessments between treatments.

There were no abnormal findings of oral cavity tolerability in any subject, with mucosa and inflammation deemed as normal in all post-dose assessments of oral cavity and sublingual space, following buprenorphine wafer administration.

On the oral symptom questionnaires, there was no sublingual irritation or burning sensation for any subject. Only one subject reported bitterness (mild) at 20 minutes postdose for administration of sublingual buprenorphine wafer 800 mcg.

Discussion

In this study the disintegration of the sublingual wafer was rapid with corresponding rapid absorption across the sublingual mucosa as shown by the early quantifiable plasma concentrations at the first pharmacokinetics sampling time point of 10 minutes. The absolute bioavailability of SL buprenorphine was 45.4% and higher than the currently approved sublingual buprenorphine tablet, Temgesic, which has a bioavailability of 35% [24]. We suspect that the lower bioavailability of the Temgesic SL tablet is due to an increased amount of buprenorphine swallowed most likely resulting from the slower disintegration profile of the tablet [19,21]. Swallowed buprenorphine undergoes extensive hepatic first-pass metabolism; the absolute bioavailability of oral buprenorphine solution was found to be 10–15% using injectable solution orally and 30% for the alcoholic solution [30–32].

The bioavailability observed with the wafer was similar to intranasal (IN) buprenorphine (48.2%) [33], although one would expect IN buprenorphine to have higher absolute bioavailability compared with SL administration. The nasal mucosa (40 to 80 μm) is thinner than the SL mucosa (100 to 200 μm) [34] and allows for faster and higher penetration of buprenorphine into the blood stream. Furthermore, IN is delivered in solution, allowing immediate absorption, whereas the SL wafer is a solid dosage form that needs saliva for complete dissolution. Conversely, the thicker SL mucosa may provide a "reservoir" effect, whereby the lipophilic buprenorphine molecules are sequestrated and then released more slowly into the blood (depot effect) [35].

A buccal buprenorphine film (Belbuca) [36] registered in some countries, showed an absolute bioavailability of 46 to 51% from doses of 75, 150, 300, 450, 600, 750, and 900 mcg [34,35], similar to the SL wafer studied here.

The $T_{max,}$ time to peak plasma buprenorphine concentration, for the SL administered wafer (one hour) was shorter than quoted for the Temgesic SL tablet (two to four hours) [24]. This again is thought to be due to the slower disintegration profile of the SL tablet. The T_{max} for the buprenorphine buccal film is three hours [21,37]. This is as expected due to the buccal mucosa being thicker (500–800 μm) than the SL mucosa (100–200 μm) and the slower release of drug from the bioerodible technology. The thicker buccal layer plus the presence of underlying smooth muscle in the buccal area of the

Table 3 Summary of treatment-emergent adverse events by treatment and Medical Dictionary for Regulatory Activities preferred term

System Organ Class	SL 800 mcg (N = 14) No. (%) [No. of TEAE]	IV 300 mcg (N = 14) No. (%) [No. of TEAE]	All (N = 14) No. (%) [No. of TEAE]
Subjects with at least 1 TEAE	8 (57) [10]	8 (57) [14]	11 (79) [24]
Blood and lymphatic system disorders	1 (7) [1]		1 (7) [1]
Lymphadenopathy	1 (7) [1]		1 (7) [1]
Psychiatric disorders		1 (7) [1]	1 (7) [1]
Nightmare		1 (7) [1]	1 (7) [1]
Nervous system disorders	4 (29) [6]	2 (14) [2]	5 (36) [8]
Headache	2 (14) [2]	1 (7) [1]	3 (21) [3]
Migraine	1 (7) [1]		1 (7) [1]
Presyncope	1 (7) [1]		1 (7) [1]
Somnolence		1 (7) [1]	1 (7) [1]
Tension headache	2 (14) [2]		2 (14) [2]
Ear and labyrinth disorders		1 (7) [1]	1 (7) [1]
Vertigo		1 (7) [1]	1 (7) [1]
Respiratory, thoracic, and mediastinal disorders		2 (14) [2]	2 (14) [2]
Bradypnoea		1 (7) [1]	1 (7) [1]
Dry throat		1 (7) [1]	1 (7) [1]
Gastrointestinal disorders	2 (14) [2]	3 (21) [4]	5 (36) [6]
Diarrhea		1 (7) [1]	1 (7) [1]
Hypoesthesia oral	2 (14) [2]		2 (14) [2]
Nausea		3 (21) [3]	3 (21) [3]
Skin and subcutaneous tissue disorders		1 (7) [2]	1 (7) [2]
Ecchymosis		1 (7) [1]	1 (7) [1]
Erythema		1 (7) [1]	1 (7) [1]
General disorders and administration site conditions	1 (7) [1]	2 (14) [2]	3 (21) [3]
Catheter site pain		2 (14) [2]	2 (14) [2]
Fatigue	1 (7) [1]		1 (7) [1]

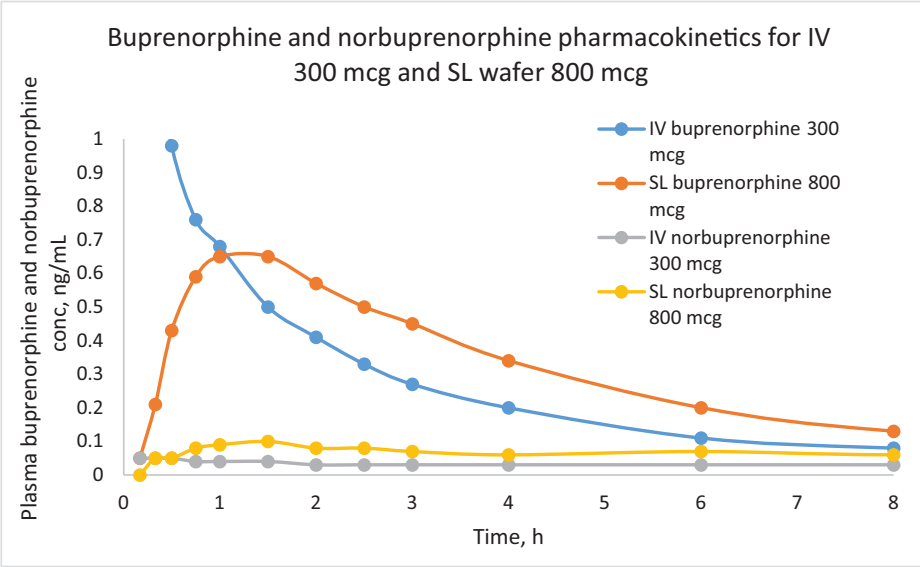

Figure 3 Plasma buprenorphine and norbuprenorphine vs time curve.

mouth provides a more retentive system and hence a slower drug absorption rate.

The C_{max} for sublingual buprenorphine 800 mcg is 0.74 ng/mL. As expected, the C_{max} for high-dose SL tablets (2–16 mg buprenorphine) is higher (1.6–6.4 ng/mL) [36–39] due to the increased buprenorphine doses. Again, this is in line with the slower absorption buccally as the buccal mucosa is thicker than the SL mucosa.

The terminal half-lives for both IV and SL adminstration were 9.1 and 11.2 hours, respectively. A single-dose study [40] of IV buprenorphine gave a terminal half-life of 5.2 hours. However, the blood sampling times for this study were only up to 10 hours compared with 48 hours with this study [40], which may account for the shorter estimated terminal half-life.

In another study [41] comparing SL buprenorphine solution with buccal film, the terminal half-lives for SL and buccal administration were reported to be 27.7 and 19.0 hours, respectively. The longer terminal half-lives may be due to a higher dose of buprenorphine 4 mg compared with this study, which used buprenorphine 800 mcg. The increasing elimination half-life with increasing buprenorphine dose has been well documented and may be contributed to by the enterohepatic recirculation of the drug. The observed half-life of 11.2 hours in this study also fell within the range (2.45–15.1 hours) observed in a dose-ranging study (75 mcg, 300 mcg, 1,200 mcg) with the buccal buprenorphine film (Belbuca). In the product information [24] for Temgesic SL 200-mcg tablets, an effective half-life of five hours is reported; a comment states that the longer elimination half-life seen in higher doses used for opioid addiction could not be detected due to the lower dosages used for analgesia.

In another report, the $T_{1/2}$ for buccal buprenorphine was 27.6 hours [21]. The buccal mucosa is thicker, with more muscle mass and adipose tissue, which may provide a "reservoir" effect, whereby the lipophilic buprenorphine molecules are initially sequestrated (retained in the buccal and mucosal tissue) and then released more slowly into the blood.

Norbuprenorphine is a weak mu agonist. A study in rats have found norbuprenorphine to be responsible for respiratory depression [42,43]. In this study (Figure 3), the ratios for C_{max} (norbuprenorphine/buprenorphine) for IV and SL administration were 2.2% and 15%.

Under a high-dose naltrexone block, subligual buprenorphine was well tolerated when administered sublingually as a single dose in this study. Treatment-emergent adverse events (TEAEs) were infrequent and largely of mild severity, as expected in antagonist-blocked patients. TEAEs were similarly distributed between sublingual buprenorphine and IV Temgesic treatment periods. The buprenorphine wafer displayed excellent local tolerability, as determined by oral examination and oral symptom questionnaires completed by participants at various time points postdosing.

Conclusions

The bioavailability of buprenorphine in the novel sublingual wafer formulation was higher than the other SL formulation available in the market. Local tolerability of the buprenorphine wafer was good. The pharmacokinetics

of buprenorphine in the novel sublingual wafer formulation showed more rapid absorption of buprenorphine than the marketed SL Temgesic, as demonstrated by the shorter T_{max} (one vs two to four hours). This results from the faster disintegration of the sublingual wafer and the release of the pharmaceutical active ingredient active into the mucosa for immediate SL absorption. This buprenorphine wafer presents a promising new formulation for both acute and chronic pain.

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