Clinical Drug Investigation (2013) 33:109–115
DOI 10.1007/s40261-012-0043-z

REVIEW ARTICLE

Pharmacokinetic Profile of Liposome Bupivacaine Injection Following a Single Administration at the Surgical Site

DeeDee Hu · Erol Onel · Neil Singla · William G. Kramer · Admir Hadzic

Published online: 11 December 2012

Abstract Local anaesthetics are often used as part of multimodal pain management techniques to manage postsurgical pain and lessen the need for opioid analgesics; however, the duration of action of traditional formulations of local anaesthetics is short. Liposome bupivacaine is a novel, multivesicular formulation designed for rapid absorption, prolonged release of bupivacaine, and analgesia following a single intra-operative administration into the surgical wound. This article provides a summary of the pharmacokinetic profile of liposome bupivacaine compared with bupivacaine HCl based on data compiled from four randomized, active- and placebo-controlled trials that included pharmacokinetic assessments following single administrations of study drug. Each study evaluated the safety, efficacy and pharmacokinetic profile of liposome bupivacaine in separate surgical populations (patients undergoing inguinal hernia repair, total knee arthroplasty, haemorrhoidectomy or bunionectomy). Pharmacokinetic parameters included maximum plasma drug concentration (C_{max}), area under the curve (AUC) for plasma bupivacaine concentration over time extrapolated to infinity (AUC_{∞}), time to observed C_{max} (t_{max}) and terminal elimination half-life of bupivacaine ($t_{½}$). The studies assessed single administrations of liposome bupivacaine at dose levels ranging from 106 to 532 mg or bupivacaine HCl 100 to 150 mg or placebo (0.9 % sodium chloride) given locally via wound infiltration at the end of surgery prior to wound closure. Male and non-pregnant female patients ($n = 253$) aged ≥18 years, scheduled to undergo surgery as per the specific protocol for each study, were enrolled. Patient characteristics were stratified by liposome bupivacaine doses ≤266 mg and >266 mg, and bupivacaine HCl treatment arms. Pharmacokinetic parameters for liposome bupivacaine doses of 106, 266, 399 and 532 mg were compared. Plasma concentration versus time profiles were quantitatively similar across these four dose levels of liposome bupivacaine, with an initial peak occurring within 1 h after administration followed by a second peak about 12–36 h later. The overall incidence of adverse events was lower in the liposome bupivacaine ≤266-mg group than the liposome bupivacaine >266-mg and bupivacaine HCl groups (100- or 150-mg doses). In summary, liposome bupivacaine was well tolerated across the four studies and varied surgical models, and exhibited bimodal kinetics with rapid uptake observed during the first few hours and prolonged release through 96 h after administration.

Electronic supplementary material The online version of this article (doi:10.1007/s40261-012-0043-z) contains supplementary material, which is available to authorized users.

D. Hu (✉)
Clinical Specialist, Critical Care and Cardiology, Memorial Hermann Memorial City Medical Center, 921 Gessner Road, Houston, TX 77024, USA
e-mail: Deedee.Hu@memorialhermann.org

E. Onel
Pacira Pharmaceuticals, Inc., Parsippany, NJ, USA

N. Singla
Lotus Clinical Research, LLC, Pasadena, CA, USA

W. G. Kramer
Kramer Consulting LLC, North Potomac, MD, USA

A. Hadzic
St. Luke's Hospital, New York, NY, USA

1 Introduction

Postsurgical pain management is a key factor in timely patient recovery after surgery [1]. Multimodal pain

management techniques (i.e., the administration of two or more analgesic medications with different analgesic mechanisms) are recommended for managing postsurgical pain to lessen the need for opioid analgesics [1, 2].

Local anaesthetics/analgesics are effective for postsurgical pain relief [3–6] and are widely used in multimodal treatment regimens for postsurgical pain management. The PROcedure-SPECific postoperative pain managemenT working group (PROSPECT) recommends that locally administered anaesthetics be used either alone or as part of multimodal pain management strategies for postsurgical analgesia in all patients undergoing haemorrhoidal surgery (Grade A recommendation) [7]. However, a major limitation of local anaesthetics, including the longer-acting local anaesthetics (e.g., bupivacaine HCl), is their relatively short duration of action (typically less than 8 h) [3, 8, 9]. The short duration of action following local administration is due to systemic absorption, limiting contact of the anaesthetic with local nerve endings. For example, bupivacaine levels reach maximum plasma drug concentration (C_{max}) in about 30–45 min (t_{max}) after a single injection of bupivacaine HCl. This is followed by a rapid decline in plasma concentrations over the next 3–6 h [10].

Liposome bupivacaine is a novel, multivesicular formulation designed for rapid absorption, prolonged release of bupivacaine, and analgesia that is maintained for up to 72 h following a single intra-operative administration into the surgical wound [11–14].

This article provides a summary of the pharmacokinetic profile of bupivacaine after administration of liposome bupivacaine compared with bupivacaine HCl based on data compiled from four phase II and III randomized, active- and placebo-controlled, multicentre trials (see Online Resource) that included pharmacokinetic assessments following single administrations of study drug [12, 13, 15, 16].

2 Description of Studies

All four studies were approved by an independent ethics committee or institutional review board and conducted in accordance with the ethical principles of the Declaration of Helsinki, in compliance with Good Clinical Practices, and applicable regulatory requirements [17, 18].

2.1 Study Design

Each of the four studies was designed to evaluate the safety, efficacy and pharmacokinetics of liposome bupivacaine (bupivacaine liposome injectable suspension, EXPAREL®; Pacira Pharmaceuticals, Inc., Parsippany, NJ, USA) in separate surgical populations at dose levels ranging from 106 to 532 mg (Table 1) [12, 13, 15, 16]. The milligram dose of liposome bupivacaine is expressed as the free base (i.e., 266 mg of bupivacaine base is chemically equivalent to 300 mg of bupivacaine HCl). All were randomized, double-blind studies that assessed single administrations of liposome bupivacaine, bupivacaine HCl (Study 1, Marcain® Polyamp Steripak, 0.5 %, AstraZeneca UK Limited, Bedfordshire, UK; Study 2, Marcaine® 0.5 % with epinephrine 1:200,000, Hospira, Inc., Lake Forest, IL, USA), or placebo (0.9 % sodium chloride) given locally via wound infiltration at the end of surgery prior to wound closure. Details of design and methodology for the studies have been reported elsewhere [12, 13, 15, 16].

2.2 Study Populations

Males and non-pregnant females aged ≥18 years scheduled to undergo inguinal hernia repair, total knee arthroplasty, haemorrhoidectomy or bunionectomy as per the specific protocol for each study were eligible to participate.

2.3 Study Procedures

In Study 1 [15], blood samples were collected to determine plasma bupivacaine concentration before study drug administration (baseline), at 5, 10, 15 and 30 min, and at 1, 2, 4, 6, 8, 12, 24, 48, 72 and 96 h after the start of study drug administration. In Study 2 [12], sample collection was done at baseline, 15 and 30 min, and at 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84 and 96 h. In Study 3 [13], samples were collected at baseline, 15 and 30 min, and at 1, 2, 4, 8, 12, 24, 36, 48, 60 and 72 h. In Study 4 [16], samples were collected at baseline, 15 and 30 min, and at 1, 2, 4, 8, 12, 24 and 72 h after study drug administration. Plasma samples were prepared from the blood samples and stored frozen (−20 °C) prior to analysis. The concentration of bupivacaine in plasma was determined using a high-performance liquid chromatography method with mass spectrometry. The lower limit of quantification of the bupivacaine assay, 0.1 ng/mL in Study 1 and 1.0 ng/mL in Studies 2, 3 and 4, was within US Food and Drug Administration (FDA)-recommended criteria for bioanalytical method validation [19].

2.4 Assessments

Pharmacokinetic parameters included C_{max} over the entire study period, area under the curve (AUC) for plasma bupivacaine concentration over time extrapolated to infinity (AUC_{∞}), t_{max}, and terminal elimination half-life of bupivacaine ($t_{½}$). Adverse events (AEs) were documented through 30 days after study drug administration in each study.

Table 1 Overview of studies

Study (identifier)	Surgical setting	No. randomized and treated	Dosages assessed	Objective
Study 1 (NCT01203644) [15]	Inguinal hernia repair	76	Liposome bupivacaine 155, 199, 266 or 310 mg, or bupivacaine HCl 100 mg	Assess safety, efficacy and PKs of liposome bupivacaine vs. bupivacaine HCl
Study 2 (NCT00485693) [12]	Total knee arthroplasty	138	Liposome bupivacaine 133, 266, 399 or 532 mg, or bupivacaine HCl 150 mg	Assess safety, efficacy and PKs of liposome bupivacaine vs. bupivacaine HCl
Study 3 (NCT00890721) [13]	Haemorrhoidectomy	189	Liposome bupivacaine 266 mg or placebo	Assess safety, efficacy and PKs of liposome bupivacaine vs. placebo (saline)
Study 4 (NCT00890682) [16]	Bunionectomy	193	Liposome bupivacaine 106 mg or placebo	Assess safety, efficacy and PKs of liposome bupivacaine vs. placebo (saline)

PKs pharmacokinetics

Table 2 Patient demographics by study and group

Parameter	Study 1 [15] (inguinal hernia repair)			Study 2 [12] (total knee arthroplasty)			Study 3 [13] (haemorrhoidectomy)	Study 4 [16] (bunionectomy)
	Liposome bupivacaine		Bupivacaine HCl	Liposome bupivacaine		Bupivacaine HCl	Liposome bupivacaine	Liposome bupivacaine
	≤266 mg *n* = 36	>266 mg *n* = 14	100 mg *n* = 26	≤266 mg *n* = 49	>266 mg *n* = 47	150 mg *n* = 30	≤266 mg *n* = 25	≤266 mg *n* = 26
Age, y [mean (SD)]								
	55 (17)	55 (13)	51 (13)	61 (8)	63 (7)	61 (7)	52 (13)	42 (15)
Age category, y [n (%)]								
<40	7 (19.4)	3 (21.4)	4 (15.4)	0	0	0	4 (16.0)	11 (42.3)
40 to < 65	18 (50.0)	7 (50.0)	19 (73.1)	30 (61.2)	24 (51.1)	20 (66.7)	16 (64.0)	14 (53.8)
≥65	11 (30.6)	4 (28.6)	3 (11.5)	19 (38.8)	23 (48.9)	10 (33.3)	5 (20.0)	1 (3.9)
Sex [n (%)]								
Male	36 (100)	14 (100)	26 (100)	23 (46.9)	16 (34.0)	10 (33.3)	17 (68.0)	6 (23.1)
Female	0	0	0	26 (53.1)	31 (66.0)	20 (66.7)	8 (32.0)	20 (76.9)
Race [n (%)]								
White	35 (97.2)	12 (85.7)	24 (92.3)	44 (89.8)	42 (89.4)	30 (100)	25 (100)	23 (88.5)
Other	1 (2.8)	2 (14.3)	2 (7.7)	5 (10.2)	5 (10.6)	0	0	3 (11.5)
ASA physical status classification [n (%)]								
1–2	36 (100)	14 (100)	26 (100)	27 (55.1)	27 (57.4)	17 (56.7)	24 (96.0)	26 (100)
3–4	0	0	0	18 (36.7)	18 (38.3)	13 (43.3)	1 (4.0)	0
Not reported	0	0	0	4 (8.2)	2 (4.3)	0	0	0

ASA American Society of Anesthesiologists, *SD* standard deviation

2.5 Statistical Analyses

In all studies, the safety population included all randomized patients who received study drug. The pharmacokinetic populations included all randomized patients in the safety population who had sufficient pharmacokinetic samples from which pharmacokinetic parameters could be estimated. For the current summary, all data were derived from the pharmacokinetic populations. Actual sampling times were used for all calculations of the pharmacokinetic parameters. Bupivacaine pharmacokinetic parameters were derived by non-compartmental analysis. Descriptive statistics (number of participants, arithmetic mean and standard deviation, and median for t_{max}) were used to summarize the pharmacokinetic data. Pharmacokinetic data were analysed using WinNonlin® version 4 in Study 1 [15], SAS® version 9.1.3 in Study 2 [12], and WinNonlin® Professional version 5.2 or later for Studies 3 [13] and 4

[16]. Frequency distributions (number and percentage of participants) were used to summarize the AEs.

3 Pharmacokinetics

For the analysis in this review, liposome bupivacaine doses were dichotomized at 266 mg, the highest FDA-approved dose. Patient characteristics from 253 patients in the four studies were stratified by liposome bupivacaine doses ≤266 mg (FDA-approved doses) and >266 mg, and bupivacaine HCl treatment arms, as shown in Table 2 [12, 13, 15, 16]. A summary of pharmacokinetic parameters for each of the 12 study arms is presented in Table 3 [12, 13, 15, 16]. Plasma bupivacaine exposure, as reflected by mean AUC_{∞} and C_{max} values, increased in a dose-proportional manner following a single administration of liposome bupivacaine over a dose range of 155 to 310 mg in Study 1 [15] (inguinal hernia) and over a dose range of 133 to 532 mg in Study 2 [12] (total knee arthroplasty). Mean C_{max} reached 935 ng/mL following administration of liposome bupivacaine 532 mg, the highest dose tested. Mean plasma bupivacaine concentrations over time for the liposome bupivacaine 106-mg treatment arm from Study 4 [16], the liposome bupivacaine 266-mg treatment arm from Study 3 [13], the liposome bupivacaine 399- and 532-mg treatment arms from Study 2, and the bupivacaine HCl 100-mg treatment arm from Study 1 are shown in Fig. 1. The shapes of the plasma concentration versus time profiles were quantitatively similar across these four dose levels of liposome bupivacaine, with an initial peak occurring within 1 h after administration followed by a second peak about 12–36 h later.

4 Tolerability and Safety

Single administrations of liposome bupivacaine were generally well tolerated in all four studies. A summary of pooled AE data for patients who received liposome bupivacaine doses ≤266 mg, >266 mg and bupivacaine HCl is presented in Table 4. The most frequently reported AEs were nausea, pyrexia, constipation, peripheral oedema, hypotension and vomiting. The overall incidence of AEs was lower in the liposome bupivacaine ≤266-mg group than in the liposome bupivacaine >266-mg and bupivacaine HCl groups (100- or 150-mg doses). Across the four studies, ten patients treated with liposome bupivacaine or bupivacaine HCl experienced 13 serious AEs. All of these serious AEs were considered unlikely to be related or not related to study drug by the study investigators.

Table 3 Summary of pharmacokinetic parameters following single doses of liposome bupivacaine and bupivacaine HCl[a]

Parameter	Study 1 [15] (inguinal hernia repair)					Study 2 [12] (total knee arthroplasty)					Study 3 [13] (haemorrhoidectomy)	Study 4 [16] (bunionectomy)
	LB 155 mg	LB 199 mg	LB 266 mg	LB 310 mg	Bup HCl 100 mg	LB 133 mg	LB 266 mg	LB 399 mg	LB 532 mg	Bup HCl 150 mg	LB 266 mg	LB 106 mg
C_{max} (ng/mL)	*n* = 12	*n* = 12	*n* = 12	*n* = 14	*n* = 26	*n* = 25	*n* = 24	*n* = 26	*n* = 21	*n* = 30	*n* = 25	*n* = 26
	241	303	365	415	336	262	340	500	935	205	867	166
	(89)	(84)	(130)	(122)	(156)	(277)	(107)	(173)	(371)	(111)	(353)	(93)
t_{max} (h)	12	10	12	12	0.6	12	24	24	36	24	0.5	2
	(0.5, 24)	(0.5, 24)	(0.6, 48)	(0.2, 49)	(0.1, 6)	(0.5, 37)	(0.5, 49)	(0.2, 48)	(2, 71)	(0.6, 48)	(0.3, 36)	(0.5, 2)
AUC_{∞} (ng•h/mL)	*n* = 12	*n* = 12	*n* = 12	*n* = 14	*n* = 26	*n* = 23	*n* = 20	*n* = 21	*n* = 19	*n* = 28	*n* = 24	*n* = 22
	9,597	10,295	16,758	19,476	4,374	7,826	17,370	27,630	60,174	7,460	18,289	7,105
	(4,370)	(4,486)	(6,288)	(8,015)	(1,561)	(3,317)	(8,540)	(12,939)	(25,117)	(4,118)	(7,569)	(2,283)
$t_{1/2}$ (h)	15.9	14.1	14.6	18.9	8.5	13.4	17.1	18.8	16.9	10.7	23.8	34.1
	(6.7)	(5.1)	(4.6)	(6.2)	(2.9)	(4.0)	(6.8)	(5.1)	(4.8)	(3.9)	(39.4)	(17.0)

[a] Values are expressed as arithmetic mean (standard deviation) except for t_{max}, which is expressed as median (range)

AUC_{∞} area under the plasma concentration time curve from time zero to infinity, *Bup* bupivacaine, *C_{max}* maximum plasma drug concentration, *LB* liposome bupivacaine, *$t_{½}$* half-life, *t_{max}* time to maximum plasma drug concentration

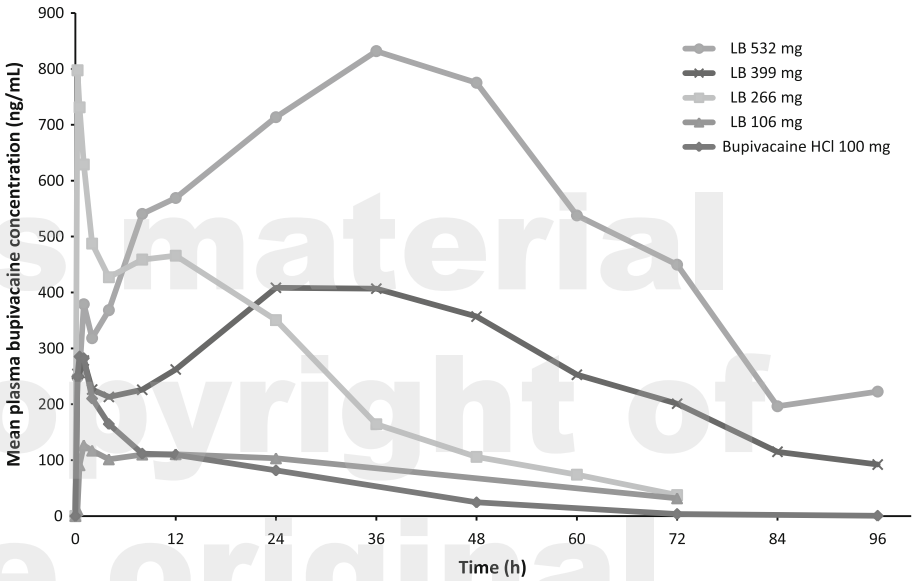

Fig. 1 Plasma bupivacaine concentration versus time for liposome bupivacaine 106, 266, 399 and 532 mg, and bupivacaine HCl 100 mg. *LB* liposome bupivacaine

5 Discussion

Liposome bupivacaine exhibited dose-proportional pharmacokinetics following single administrations via wound infiltration at dose levels up to 532 mg. Liposome bupivacaine contains a small amount of extra-liposomal bupivacaine (about 3 %) to allow for fast onset, similar to bupivacaine HCl. The remainder of bupivacaine is encapsulated in multivesicular liposomes that slow and prolong release of bupivacaine. Thus, the mean plasma concentration versus time curves derived from four study arms, representing liposome bupivacaine doses that ranged from 106 to 532 mg in different surgical models, all exhibited the bimodal release profile of this novel formulation (Fig. 1). Indeed, the levels were characterized with an initial peak soon after administration of study drug (associated with extra-liposomal bupivacaine), followed by a later peak (associated with release of the liposome-encapsulated bupivacaine) that occurred within 10–36 h after administration. The rate of systemic absorption of bupivacaine is dependent upon the total dose administered, route of administration and vascularity at the site of drug administration [20].

The sustained plasma bupivacaine concentration levels observed over time suggest that the liposomes gradually release bupivacaine at the site of local injection. Although it is unknown if systemic plasma concentrations correlate with local efficacy, recent evidence reported with liposome bupivacaine has demonstrated analgesia for up to 72 h after a single injection via local infiltration as compared with bupivacaine HCl or placebo [11–14]. A pooled analysis from ten clinical studies of single administrations of liposome bupivacaine in various surgical settings ($n = 1{,}459$) showed that liposome bupivacaine significantly extended median time to first use of postsurgical opioid medication by about 6 h longer than placebo and 3 h longer than bupivacaine HCl [21].

Liposome bupivacaine and bupivacaine HCl are not bioequivalent even when the milligram doses are the same. They are not, therefore, interchangeable [20]. The highest FDA-approved dose of liposome bupivacaine (266 mg) is about two to three times the commonly used dosage of bupivacaine HCl for single administrations into surgical wounds. Study 1, which assessed comparative efficacy and single-dose pharmacokinetics in inguinal hernia repair, showed that a three-fold higher liposome bupivacaine dose (266 mg) produced a similar C_{max} to bupivacaine HCl 100 mg, but the liposome bupivacaine formulation had a longer release profile than bupivacaine HCl (as reflected by its four-fold greater AUC).

Liposome bupivacaine was generally well tolerated across the four studies in this analysis, and the tolerability results observed here are consistent with the tolerability profile observed in other clinical studies of this agent [11, 14]. As expected, the incidence of AEs was generally lower in treatment groups that received lower doses of liposome bupivacaine compared with groups that received higher doses. The maximum dose of liposome bupivacaine assessed in these four wound infiltration studies (532 mg in Study 2) [12] produced a mean C_{max} of 935 ng/mL, below the threshold range (2,000–4,000 ng/mL) at which central nervous system and cardiovascular toxicity are expected to occur [22, 23]. The highest mean C_{max} observed following administration of liposome bupivacaine 266 mg, the highest FDA-approved dose, was 867 ng/mL (Study 3) [13]. No signs of neuro- or cardiac toxicity have been

Table 4 Summary of adverse events [n (%)] occurring in ≥5 % of patients[a]

Adverse event	Liposome bupivacaine ≤266 mg, *n* = 136	Liposome bupivacaine >266 mg, *n* = 61	Bupivacaine HCl *n* = 56
Any adverse event	77 (56.6)	45 (73.8)	41 (73.2)
Nausea	34 (25.0)	25 (41.0)	21 (37.5)
Constipation	20 (14.7)	14 (23.0)	12 (21.4)
Pyrexia	20 (14.7)	18 (29.5)	11 (19.6)
Hypotension	14 (10.3)	9 (14.8)	11 (19.6)
Peripheral oedema	14 (10.3)	13 (21.3)	9 (16.1)
Haemorrhagic anaemia	4 (2.9)	9 (14.8)	6 (10.7)
Pruritus	6 (4.4)	1 (1.6)	6 (10.7)
Vomiting	15 (11.0)	6 (9.8)	6 (10.7)
Anaemia postoperative	10 (7.4)	2 (3.3)	5 (8.9)
Dizziness	11 (8.1)	7 (11.5)	5 (8.9)
Insomnia	4 (2.9)	5 (8.2)	5 (8.9)
Headache	5 (3.7)	2 (3.3)	4 (7.1)
Fatigue	1 (0.7)	5 (8.2)	4 (7.1)
Decreased appetite	0	0	3 (5.4)
Muscle spasms	5 (3.7)	0	3 (5.4)
Tachycardia	9 (6.6)	7 (11.5)	3 (5.4)
Anaemia	2 (1.5)	7 (11.5)	2 (3.6)
Hypertension	3 (2.2)	2 (3.3)	2 (3.6)
Hypoaesthesia	3 (2.2)	1 (1.6)	2 (3.6)
Hypokalaemia	1 (0.7)	0	2 (3.6)
Localized oedema	0	0	2 (3.6)
Oropharyngeal pain	2 (1.5)	1 (1.6)	2 (3.6)
Presyncope	0	1 (1.6)	2 (3.6)
Urinary retention	3 (2.2)	2 (3.3)	2 (3.6)
Wound infection	0	0	2 (3.6)
Somnolence	8 (5.9)	3 (4.9)	1 (1.8)
Cough	4 (2.9)	2 (3.3)	1 (1.8)
Asthenia	3 (2.2)	2 (3.3)	1 (1.8)
Bradycardia	2 (1.5)	3 (4.9)	1 (1.8)
Anxiety	1 (0.7)	3 (4.9)	1 (1.8)
Dyspepsia	1 (0.7)	2 (3.3)	1 (1.8)
Joint swelling	0	3 (4.9)	1 (1.8)
Confusional state	0	2 (3.3)	1 (1.8)
Erythema	0	2 (3.3)	1 (1.8)
Incision site haemorrhage	0	2 (3.3)	1 (1.8)
Blood glucose increased	2 (1.5)	2 (3.3)	0
Dyspnoea exertional	0	2 (3.3)	0
Incision site oedema	0	2 (3.3)	0
Lethargy	3 (2.2)	2 (3.3)	0

[a] Adverse events were defined as any untoward medical occurrence that occurred after the beginning of study drug administration, regardless of whether its occurrence was considered causally related to the study drug

observed in the studies of liposome bupivacaine conducted to date [24, 25].

The studies described in our analysis have several limitations. The study populations were small and comprised relatively healthy patients (most had an American Society of Anesthesiologists physical status of 1 or 2) who were not taking multiple concomitant medications. Potential effects of co-morbidities and drug-drug interactions on the pharmacokinetic profile of liposome bupivacaine were not taken into account, although pharmacokinetic data from individuals with moderate hepatic impairment showed that dosage modification is not needed in these patients [26]. It should be noted that since liposome bupivacaine is administered and acts locally, assessments of systemic pharmacokinetics were used as a proxy for local pharmacokinetics at surgical sites involved in the study procedures.

6 Conclusions

The pharmacokinetic profile of liposome bupivacaine differs from that of bupivacaine HCl. Liposome bupivacaine consistently exhibited bimodal kinetics across several surgical models. The formulation resulted in a rapid uptake of bupivacaine during the first few hours after administration, and prolonged release as reflected in assessments of systemic plasma concentrations measured through 96 h. The shapes of plasma bupivacaine concentration curves over time were also consistent across the various doses tested, although C_{max} varied depending on dose and vascularity of the surgical model.

Acknowledgements This analysis was funded by Pacira Pharmaceuticals, Inc. DeeDee Hu is a member of an advisory board for Pacira Pharmaceuticals, Inc. Erol Onel is an employee and owns stock in Pacira Pharmaceuticals, Inc. Neil Singla has received a research grant from Pacira Pharmaceuticals, Inc. William G. Kramer has been a paid consultant to Pacira Pharmaceuticals, Inc. Admir Hadzic has received research grants and honoraria as a consultant for Baxter International Inc., Cadence Pharmaceuticals Inc., Macosta Medical USA, LLC, and Pacira Pharmaceuticals, Inc. Editorial assistance was provided by Michael Morren, RPh, MBA, of Peloton Advantage, LLC, supported by Pacira Pharmaceuticals, Inc.

References

1. Apfelbaum JL. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012;116(2):248–73.
2. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol. 2009;22(5):588–93.
3. Jirasiritham S, Tantivitayatan K, Jirasiritham S. Perianal blockage with 0.5% bupivacaine for postoperative pain relief in hemorrhoidectomy. J Med Assoc Thai. 2004;87(6):660–4.

4. Mahabir RC, Peterson BD, Williamson JS, et al. Locally administered ketorolac and bupivacaine for control of postoperative pain in breast augmentation patients. Plast Reconstr Surg. 2004;114(7):1910–6.
5. Moiniche S, Mikkelsen S, Wetterslev J, et al. A qualitative systematic review of incisional local anaesthesia for postoperative pain relief after abdominal operations. Br J Anaesth. 1998;81(3): 377–83.
6. Kastrissios H, Triggs EJ, Sinclair F, et al. Plasma concentrations of bupivacaine after wound infiltration of an 0.5% solution after inguinal herniorrhaphy: a preliminary study. Eur J Clin Pharmacol. 1993;44(6):555–7.
7. Joshi GP, Neugebauer EA, on behalf of the PROSPECT Collaboration. Evidence-based management of pain after haemorrhoidectomy surgery. Br J Surg. 2010;97(8):1155–68.
8. Chester JF, Stanford BJ, Gazet JC. Analgesic benefit of locally injected bupivacaine after hemorrhoidectomy. Dis Colon Rectum. 1990;33(6):487–9.
9. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology. 2002; 96(3):725–41.
10. Bupivacaine hydrochloride [package insert]. Lake Forest, IL: Hospira, Inc.; 2010.
11. Haas E, Onel E, Miller H, et al. A double-blind, randomized, active-controlled study for post-hemorrhoidectomy pain management with liposome bupivacaine, a novel local analgesic formulation. Am Surg. 2012;78(5):574–81.
12. Bramlett K, Onel E, Viscusi ER, et al. A randomized, double-blind, dose-ranging study comparing wound infiltration of DepoFoam bupivacaine, an extended-release liposomal bupivacaine, to bupivacaine HCl for postsurgical analgesia in total knee arthroplasty. Knee. 2012;19(5):530–6.
13. Gorfine SR, Onel E, Patou G, et al. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Dis Colon Rectum. 2011;54(12):1552–9.
14. Smoot JD, Bergese SD, Onel E, et al. The efficacy and safety of DepoFoam® bupivacaine in patients undergoing bilateral, cosmetic, submuscular augmentation mammoplasty: a randomized, double-blind, active-control study. Aesthet Surg J. 2012;32(1): 69–76.
15. Langford RM, Chappell GM, Karrasch JA. A single administration of DepoBupivacaine intraoperatively results in prolonged detectable plasma bupivacaine and analgesia in patients undergoing inguinal hernia repair [abstract P-9088]. Presented at: Annual Postgraduate Assembly in Anesthesiology of the New York State Society of Anesthesiologists; 2008 Dec 12–16; New York (NY).
16. Golf M, Daniels SE, Onel E. A phase 3, randomized, placebo-controlled trial of DepoFoam(R) bupivacaine (extended-release bupivacaine local analgesic) in bunionectomy. Adv Ther. 2011;28(9):776–88.
17. International Conference on Harmonisation Working Group. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; June 10, 1996; Washington, DC [online]. Available from URL: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf. Accessed April 19, 2012.
18. World Medical Association. Declaration of Helsinki: ethical principles for medical research involving human subjects [online]. Available from URL: http://www.wma.net/en/30publications/10policies/b3/17c.pdf. Accessed April 19, 2012.
19. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Veterinary Medicine. Guidance for Industry: Bioanalytical Method Validation. 2001 May 1.
20. Exparel [package insert]. San Diego, CA: Pacira Pharmaceuticals, Inc.; 2011.
21. Bergese SD, Ramamoorthy S, Patou G, et al. Efficacy profile of liposome bupivacaine, a novel formulation of bupivacaine for postsurgical analgesia. J Pain Res. 2012;5:107–16.
22. Jorfeldt L, Lofstrom B, Pernow B, et al. The effect of local anaesthetics on the central circulation and respiration in man and dog. Acta Anaesthesiol Scand. 1968;12(4):153–69.
23. Bardsley H, Gristwood R, Baker H, et al. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol. 1998;46(3):245–9.
24. Naseem A, Harada T, Wang D, et al. Bupivacaine extended release liposome injection does not prolong QTc interval in a thorough QT/QTc study in healthy volunteers. J Clin Pharmacol. 2012;52(9):1441–7.
25. Bergese SD, Onel E, Morren M, et al. Bupivacaine extended-release liposome injection exhibits a favorable cardiac safety profile. Reg Anesth Pain Med. 2012;37(2):145–51.
26. Onel E, Warnott K, Markvicka T, et al. Pharmacokinetics of depobupivacaine (EXPAREL™), a novel bupivacaine extended-release liposomal injection, in volunteers with moderate hepatic impairment [abstract]. Clin Pharmacol Ther. 2011;89(Suppl 1):S28–9.