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Safety and Side Effect Profile of Liposome Bupivacaine (Exparel) in Peripheral Nerve Blocks

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Background: Liposome bupivacaine (Exparel) is a multivesicular liposomal formulation of bupivacaine currently approved in the United States for single-dose administration into the surgical site to provide postsurgical analgesia. This retrospective analysis examined safety data from clinical trials involving the off-label use of this formulation in peripheral nerve blocks.

Methods: Data from 6 controlled (phases I-III) studies were compiled involving single-injection ankle, femoral nerve, and intercostal nerve blocks (2 each). Adverse events (AEs) were monitored for 1 to 30 days after study drug administration.

Results: Of 575 subjects, 335 received liposome bupivacaine (2–310 mg), 33 received bupivacaine HCl (75–125 mg), and 207 received normal saline (placebo). Overall, 76% of subjects receiving liposome bupivacaine experienced 1 or more AEs compared with 61% receiving bupivacaine HCl and 76% receiving placebo. The most frequently reported AEs among subjects receiving liposome bupivacaine were nausea, pyrexia, pruritus, constipation, and vomiting. The most common treatment-related AE was hypesthesia among subjects treated with liposome bupivacaine or bupivacaine HCl. Incidence of nervous system AEs for liposome bupivacaine, bupivacaine HCl, and placebo was 21%, 27%, and 21%, respectively. Similarly, incidence of cardiac AEs was 9%, 0%, and 12%, respectively. At least 1 serious AE occurred in 8% of subjects receiving liposome bupivacaine compared with 10% of those receiving placebo (none assessed by investigators as related to study medication).

Conclusions: Liposome bupivacaine has a similar safety and side effect profile to bupivacaine HCl and normal saline, suggesting that most of the more common AEs are related to either opioid rescue or the surgical procedure itself.

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Liposomal technology for delivery of local anesthetics has been used since the 1970s.[1] Structurally, microscopic liposome vesicles are formed when lipid molecules with a hydrophilic "head" and 2 hydrophobic "tails" are suspended in an aqueous medium, resulting in an aqueous compartment encapsulated by lipid bilayers that contain entrapped substances.[1] As such, liposomal formulations can be used as vehicles to deliver medication to specific targets while avoiding high plasma levels and/or systemic toxicity.[1,2]

DepoFoam is a drug delivery system that prolongs drug release by encapsulating the drug in multivesicular liposomes made up of nonconcentric multiple lipid layers.[3–6] The lipid layers in DepoFoam are composed of biodegradable phospholipids, cholesterol, and triglycerides.[5,7,8] The rate of drug release can vary based on the characteristics of the lipid membrane components and the encapsulated aqueous phase, as well as the milieu in which DepoFoam is suspended.[5]

One formulation of liposome bupivacaine (bupivacaine liposome injectable suspension [Exparel]; Pacira Pharmaceuticals, Inc, Parsippany, New Jersey), based on DepoFoam technology,

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Work should be attributed the all authors' institutions.

B.M.I. was involved with study design, execution, and data collection; analysis/interpretation of data and manuscript drafting/revising, review, and final approval. E.R.V. was involved with the analysis/interpretation of data, drafting/revising of the manuscript, review, and final approval. A.H. was involved with contribution of vital reagents/tools/patents, acquisition of data, statistical analysis, and study supervision or coordination, manuscript review, and final approval. H.S.M. was involved in the analysis or interpretation of data, drafting/revising the manuscript for content including medical writing, had access to all data used in this study, gave final approval of the version to be published, and takes overall responsibility for the data and the accuracy of the manuscript. M.D.M. was involved in literature searching, writing, and editorial revisions based on coauthor feedback throughout the manuscript preparation process and final approval. J.L. was involved with the acquisition of data, statistical analysis and interpretation of data, along with the drafting/revising of the manuscript, review, and final approval. G.P.J. was involved with the analysis/interpretation of data, drafting/revising of the manuscript, review, and final approval. The authors are fully responsible for the content, editorial decisions, and opinions expressed in the current article.

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TABLE 1. Overview of Included Clinical Trials

Study/NIH Identifier/NIH Registration Date	Phase	Site-Specific Primary Investigator(s)	Type of Block	Population/ Surgical Procedure	Study Design	Treatment Groups*		Total No. of Subjects (Safety Population)
						Liposome Bupivacaine	Comparator	
1†	I	T. Mant, C. Brindley	Ankle	Healthy volunteers	Randomized, double masked, active controlled	67 mg (n = 6) 111 mg (n = 7) 133 mg (n = 6) 155 mg (n = 6) (15 mL)	Bupivacaine HCl 75 mg (n = 12) (15 mL)	37
2 NCT01206595/ Sep 19, 2010	II	A. Houston, B. Forster, D. Colquhoun, F. Singelyn, R. Heylen, S. Goossens, E. Vander-meersch, M. Struys, R. van Seventer, M. A. Emanuel, A. Binning, K. Milligan, R. Langford, C. Mugglestone	Ankle	Bunionectomy	Randomized, double masked, active controlled	155 mg (n = 12) 200 mg (n = 12) 310 mg (n = 14) (25 mL)	Bupivacaine HCl 125 mg (n = 20) (25 mL)	58
3 NCT01349140/ May 4, 2011	I	B. Ilfeld	Femoral[17]	Healthy volunteers	Prospective, double masked, placebo controlled, dose-response	2 mg (n = 1) 4 mg (n = 1) 10 mg (n = 1) 13 mg (n = 1) 27 mg (n = 1) 53 mg (n = 1) 62 mg (n = 1) 71 mg (n = 2) 89 mg (n = 1) 106 mg (n = 1) 124 mg (n = 3) (30 mL)	Placebo (n = 4)‡ (30 mL)	14
4 NCT01683071/ Sep 7, 2012	II–III	T. Melson, C. Hartrick, J. C. Restrepo, H. Minkowitz, D. Leiman, R. Berkowitz, J. Bracken, M. Hollmann, A. Turan, B. Ilfeld, A. Uskova, A. Hadzic, D. Hardman, H.Williams, R. Setzler, E. J. Dabezies, Jr, D. Eloy, S. Styles, S. Ayad, S. Adhikary, K. Candiotti, J. Gimbel, F. Ringold	Femoral	Total knee arthroplasty	Randomized, double masked, parallel group, placebo controlled, dose-response	67 mg (n = 22) 133 mg (n = 24) 266 mg (n = 116) (20 mL)	Placebo (n = 116) (20 mL)	278
5 NCT00807209/ Dec 9, 2008	II	H. Minkowitz, C. Anderson	Intercostal	Thoracotomy	Randomized, double masked, active controlled	67 mg (n = 1) 133 mg (n = 1) (12 mL)	Bupivacaine HCl 120 mg (n = 1) (12 mL)	3

Continued next page

TABLE 1. (*Continued*)

Study/NIH Identifier/NIH Registration Date	Phase	Site-Specific Primary Investigator(s)	Type of Block	Population/ Surgical Procedure	Study Design	Treatment Groups*		Total No. of Subjects (Safety Population)
						Liposome Bupivacaine	Comparator	
6 NCT01802411/ Feb 26, 2013	III	C. Dyke, H. Minkowitz, D. Nichols, A. Rao, D. Petrov, T. Stefanov, A. Tcher-veniakov, D. Yordanov, T. Bohanes, V. Hytych, J. Skach, D. Giorgadze, S. Gogishvili, V. Katsarava, M. Brocki, M. Glogowski, J. Bartosz Kubisa, H. Misiolek	Intercostal	Thoracotomy	Randomized, double masked, parallel group, placebo controlled	266 mg (n = 94) (20 mL)	Placebo (n = 91) (20 mL)	185

*Liposome bupivacaine doses shown in the table are expressed as the free base.
†NIH registration information not available for study 1.
‡The total number of subjects in this study was 14; subjects in the placebo group also received liposome bupivacaine.
NIH indicates National Institutes of Health.

was approved by the US Food and Drug Administration (FDA) in 2011. It is indicated exclusively for single-dose administration into the surgical site to produce postsurgical analgesia in adults.[9] Several randomized, double-masked, controlled, single-dose wound infiltration studies have demonstrated its efficacy for various surgical procedures.[10–13] In these studies, liposome bupivacaine reduced postsurgical pain intensity scores and opioid consumption for up to 72 hours, with a safety profile similar to that of bupivacaine HCl and placebo.[14]

More recently, the manufacturer has completed multiple clinical trials investigating the use of liposome bupivacaine in peripheral nerve blocks and has submitted these data as part of an application to the FDA to expand the indications for liposome bupivacaine to include such use. We therefore performed a retrospective analysis by pooling the safety data produced by 6 phases I to III clinical studies in which this specific formulation was used in a peripheral nerve block.

METHODS

Safety data were pooled from 6 phases I to III studies of liposome bupivacaine used in peripheral nerve blocks (Table 1). Each individual study was performed in compliance with the Declaration of Helsinki and its amendments and was conducted according to the principles of good clinical practice.[15,16] The studies were sponsored by Pacira Pharmaceuticals, Inc, in support of a supplemental new drug application submitted to the FDA. All subjects provided written informed consent, and each study site obtained approval from an institutional review board or ethics committee before any study procedures were conducted. In addition, an institutional review board (University of California, San Diego, San Diego, California) approved the pooling and analysis of these data.

Because the use of liposome bupivacaine as part of a peripheral nerve block is an off-label use, an Investigational New Drug approval was attained from the FDA prior to enrollment for each study (Investigational New Drug application no. 69,198). Safety data were collected by the original investigators on the day of study drug administration and the following 1 to 30 days.

Evaluations

Treatment-emergent adverse events (AEs), defined as events with an onset date/time on or after the start of study drug administration, were coded using MedDRA (Medical Dictionary for Regulatory Activities) version 14.1. Hereafter, treatment-emergent AEs will be referred to simply as "AEs." Adverse event data were collected for up to 30 days after study drug administration and have been pooled for this analysis. Subjects experiencing more than 1 episode of a particular AE were counted only once for that event. Adverse events that were considered by investigators to be possibly related, probably related, or related to study drug were classified as treatment-related AEs. In addition, AEs of special interest—defined as those associated with nervous system or cardiovascular system reactions—were individually assessed. Such AEs included syncope, grand mal convulsion, loss of consciousness, confusional state, atrial fibrillation, cardiac failure congestive, angina pectoris, diastolic dysfunction, myocardial infarction, ventricular tachycardia, arrhythmia, and cardiomegaly).

All AEs were summarized using frequency counts and percentages (n [%]) of subjects by treatment group. Percentages were calculated using the number of subjects in the safety population, defined as all subjects who received any amount of study drug. Subjects in the liposome bupivacaine group were categorized by dosage received (<266 mg, 266 mg [the maximum FDA-approved dose], and >266 mg). Because of the relatively small sample size

TABLE 2. Baseline Subject Demographics

Parameter	Liposome Bupivacaine <266 mg (n = 111)	Liposome Bupivacaine 266 mg* (n = 210)	Liposome Bupivacaine >266 mg (n = 14)	Liposome Bupivacaine All Doses (n = 335)	Bupivacaine HCl (n = 33)	Placebo (n = 207)
Age, mean (SD), y	51 (20)	63 (12)	52 (15)	58 (16)	46 (19)	62 (12)
Age category, n (%)						
<40 years	37 (33)	10 (5)	2 (14)	49 (15)	13 (39)	9 (4)
40 to <65 y	36 (32)	105 (50)	9 (64)	150 (45)	14 (42)	111 (54)
≥65 y	38 (34)	95 (45)	3 (21)	136 (41)	6 (18)	87 (42)
Male, n (%)	57 (51)	114 (54)	6 (43)	177 (53)	14 (42)	105 (51)
Ethnicity, n (%)						
Hispanic or Latino	3 (3)	14 (7)	0	17 (5)	0	15 (7)
Not Hispanic or Latino	59 (53)	196 (93)	0	255 (76)	1 (3)	192 (93)
Not reported	49 (44)	0	14 (100)	63 (19)	32 (97)	0
Race, n (%)						
White	95 (86)	190 (91)	14 (100)	299 (89)	32 (97)	187 (90)
Not white	16 (14)	20 (10)	0	36 (11)	1 (3)	20 (10)
ASA physical status classification, n (%)						
1–2	91 (82)	139 (66)	14 (100)	244 (73)	32 (97)	141 (68)
3–4	20 (18)	71 (34)	0	91 (27)	1 (3)	66 (32)

*Maximum US FDA–approved dose.

ASA indicates American Society of Anesthesiologists.

in the liposome bupivacaine >266 mg and bupivacaine HCl groups, between-group statistical comparisons were not performed.

RESULTS

Five studies were randomized, double masked, and active or placebo controlled, whereas the sixth was a double-masked, dose-response study (Table 1). Two studies enrolled healthy volunteers, whereas the others involved subjects who underwent bunionectomy, total knee arthroplasty, or thoracotomy (Table 1). There were 2 studies each involving ankle, femoral nerve,[17] and intercostal blocks (Table 1).

Subjects

A total of 575 subjects were enrolled across the 6 studies (Table 2). Of these, 335 subjects received liposome bupivacaine doses ranging from 2 to 310 mg for ankle, femoral, or intercostal nerve block. The majority (63%) received liposome bupivacaine 266 mg, whereas 111 (33%) received a lower dose, and 14 (4%) received a higher dose. Thirty-three subjects received bupivacaine HCl, and 207 were given placebo. In total, 11% of subjects (63/575) withdrew prior to study completion, including 9% (30/335) in the liposome bupivacaine groups, 6% (2/33) in the bupivacaine HCl group, and 15% (31/207) in the placebo group.

Adverse Events

Overall, 76% of subjects receiving liposome bupivacaine experienced 1 or more AEs, compared with 61% receiving bupivacaine HCl and 76% of those receiving placebo (Table 3). Almost all AEs were mild to moderate in severity, and no serious AEs were considered related to study drug. There were 6 deaths (4 in the placebo group; 2 in the liposome bupivacaine group), all of which occurred in the phase III thoracotomy study (study 6), but none of these were considered related to study drug by the investigators.

The most common AEs overall in the liposome bupivacaine group were nausea, pyrexia, constipation, vomiting, and pruritus

TABLE 3. Adverse Events

Parameter	Liposome Bupivacaine <266 mg (n = 111)	Liposome Bupivacaine 266 mg (n = 210)	Liposome Bupivacaine >266 mg (n = 14)	Liposome Bupivacaine All Doses (n = 335)	Bupivacaine HCl (n = 33)	Placebo (n = 207)
Any AE, n (%)	83 (75)	165 (79)	8 (57)	256 (76)	20 (61)	157 (76)
Maximum severity, n (%)*						
Mild	51 (61)	75 (45)	5 (62)	131 (51)	15 (75)	72 (46)
Moderate	29 (35)	78 (47)	3 (38)	110 (43)	4 (20)	63 (40)
Severe	3 (4)	12 (7)	0	15 (6)	1 (5)	22 (14)
Any serious AE, n (%)	7 (6)	21 (10)	0	28 (8)	0	21 (10)
Deaths,† n (%)	0	2 (1)	0	2 (0.6)	0	4 (2)

*Percentage based on total number of subjects with any AE.

†No serious AEs or deaths were assessed by study investigators as related to study drug.

TABLE 4. Adverse Events Reported in More Than 10% of Subjects in Any Group

Sign or Symptom	Liposome Bupivacaine				Bupivacaine HCl (n = 33)	Placebo (n = 207)
	<266 mg (n = 111)	266 mg (n = 210)	>266 mg (n = 14)	All Doses (n = 335)		
Nausea	31 (28)	64 (31)	1 (7)	96 (29)	3 (9)	74 (36)
Pyrexia	17 (15)	51 (24)	0	68 (20)	2 (6)	39 (19)
Constipation	6 (5)	38 (18)	1 (7)	45 (13)	0	35 (17)
Vomiting	5 (5)	28 (13)	0	33 (10)	0	44 (21)
Pruritus	6 (5)	35 (17)	0	41 (12)	0	33 (16)
Dizziness	6 (5)	20 (10)	0	26 (8)	0	26 (13)
Hypesthesia	21 (19)	5 (2)	0	26 (8)	8 (24)	1 (0.5)
Paresthesia	6 (5)	1 (0.5)	0	7 (2)	4 (12)	0
Bradycardia	1 (1)	4 (2)	2 (14)	7 (2)	0	2 (1)

Values are reported as the number of subjects (percentage of treatment group).

(Table 4). Among subjects who received the FDA maximum recommended liposome bupivacaine dose of 266 mg in the phase III studies, the most common AEs were nausea, pyrexia, pruritus, and constipation (Fig. 1). Incidence of AEs was similar in the liposome bupivacaine 266 mg and placebo groups.

Treatment-related AEs were reported in 13% of subjects who received liposome bupivacaine, 36% receiving bupivacaine HCl, and 2% for those who received placebo (Table 5). The most common treatment-related AE in the liposome bupivacaine and bupivacaine HCl groups was hypesthesia (7% and 24%, respectively); vomiting (1%) was the most common treatment-related AE in the placebo group.

The overall incidence of nervous system AEs was 21% in subjects receiving liposome bupivacaine, 27% in the bupivacaine HCl group, and 21% in the placebo group (Table 6). The most common nervous system–related AEs were hypesthesia and dizziness. The overall incidence of cardiac-related AEs was 9% in subjects receiving liposome bupivacaine, 0% in the bupivacaine HCl group, and 12% in the placebo group (Table 6). The most commonly reported cardiac-related AEs were bradycardia and sinus tachycardia.

Among the subjects who received the maximum recommended liposome bupivacaine dose (266 mg) in the phase III studies and experienced cardiac AEs, 9 had corresponding C_{max} values available; all 9 were in study 6. The mean C_{max} value for these subjects was 820 (SD, 501) ng/mL compared with a mean C_{max} of 794 (SD, 510) ng/mL in the overall subject population in study 6. Of the 9 subjects, only 2 subjects had documented electrocardiogram (ECG) changes from baseline to the time at which C_{max} occurred (T_{max}); 1 subject who experienced hypertension had a C_{max} of 244 ng/mL, and 1 subject who experienced increased heart rate had a C_{max} of 1820 ng/mL. Both of these subjects had a normal ECG at baseline and an abnormal ECG at T_{max}. The greatest mean general-population C_{max} value observed across all of the studies included in the current analysis was 794 (SD, 510) ng/mL, which occurred following administration of a liposome bupivacaine dose of 266 mg in study 6; this is well below the threshold range (2000–4000 ng/mL) at which central nervous system and cardiovascular AEs would be expected to occur.[18,19]

Overall, AE rates were similar in subgroups stratified by age, gender, ethnicity, or race, with no clinically meaningful differences identified. A higher incidence of AEs was observed in the group 65 years or older (85%) compared with younger age groups for subjects who received liposome bupivacaine (<73%) or placebo (82%), with too few subjects in the bupivacaine HCl group to be compared.

DISCUSSION

This retrospective study pooling 6 prospective clinical trials that used liposome bupivacaine in peripheral nerve blocks suggests

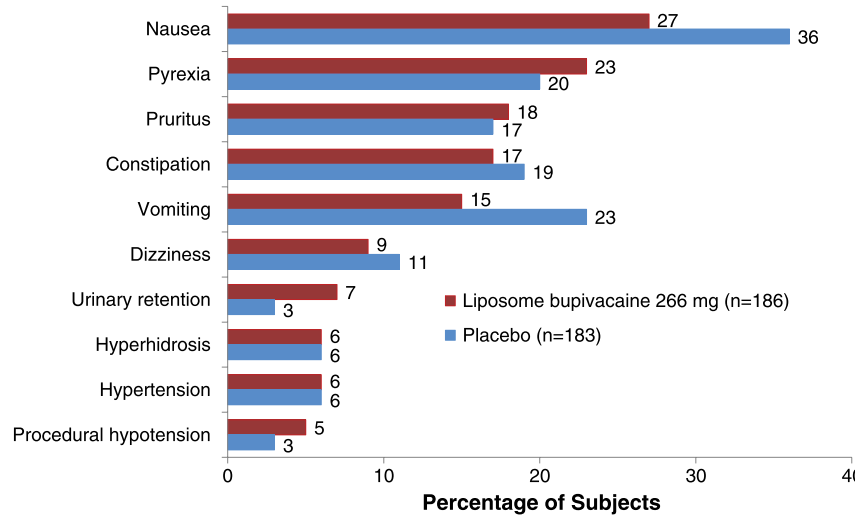

FIGURE 1. Adverse events occurring in 5% of subjects or more receiving liposome bupivacaine 266 mg in phase III studies.

TABLE 5. Treatment-Related AEs Reported in 1% of Subjects or More in Any Group

Sign or Symptom	Liposome Bupivacaine <266 mg (n = 111)	Liposome Bupivacaine 266 mg (n = 210)	Liposome Bupivacaine >266 mg (n = 14)	Liposome Bupivacaine All Doses (n = 335)	Bupivacaine HCl (n = 33)	Placebo (n = 207)
Any treatment-related AE	31 (28)	12 (6)	0	43 (13)	12 (36)	4 (2)
Hypesthesia	21 (19)	1 (0.5)	0	22 (7)	8 (24)	0
Paresthesia	6 (5)	0	0	6 (2)	3 (9)	0
Arthralgia	4 (4)	0	0	4 (1)	0	1 (0.5)
Injection site erythema	1 (0.9)	0	0	1 (0.3)	3 (9)	0
Pain in extremity	3 (3)	1 (0.5)	0	4 (1)	0	0
Headache	2 (2)	0	0	2 (0.6)	1 (3)	0
Hypotension	0	1 (0.5)	0	1 (0.3)	2 (6)	0
Pruritus	3 (3)	0	0	3 (0.9)	0	0
Bradycardia	0	2 (1)	0	2 (0.6)	0	0
Injection site discomfort	1 (0.9)	0	0	1 (0.3)	1 (3)	0
Mobility decreased	0	2 (1)	0	2 (0.6)	0	0
Muscular weakness	0	2 (1)	0	2 (0.6)	0	0
Vomiting	0	0	0	0	0	2 (1)

Values are reported as the number of subjects (percentage of treatment group).

that this liposome bupivacaine formulation has a similar safety and side effect profile to bupivacaine HCl and placebo (normal saline). To our knowledge, the 6 studies included in this analysis comprise all safety data available regarding the use of this formulation for peripheral nerve block in humans. It is emphasized that no liposome bupivacaine formulation—including EXPAREL—is approved by the FDA for use in peripheral nerve blocks; such use must be considered experimental until an FDA approval is issued. In addition, the relatively small number of subjects in the current study limits our ability to draw definitive conclusions, especially involving extraordinarily rare AEs.

Preclinical Safety Data

Myotoxicity and neurotoxicity are potential concerns with high doses of local anesthetics,[20] and some controlled-release formulations of local anesthetics have been associated with myotoxicity in animals, even at low drug concentrations.[21,22] Data from preclinical studies conducted to date have shown a single administration of liposome bupivacaine in peripheral nerve block to be generally well tolerated, with no signs of neurotoxicity observed in the animal models tested.[23,24] In a study of liposome bupivacaine 25 mg/kg (1.33%) versus bupivacaine HCl 10 mg/kg (0.5%) or 25 mg/kg (1.31%) for sciatic nerve blockade in rats, McAlvin et al[23] reported liposome bupivacaine and bupivacaine HCl 0.5% to be associated with similar levels of myotoxicity at 4 days after study drug administration, with both of these groups exhibiting less myotoxicity than the bupivacaine HCl 1.33% group. Myotoxicity was similar in all 3 treatment groups at 2 weeks after dose. The liposome bupivacaine group exhibited slightly higher levels of inflammation than did the bupivacaine HCl groups at 4 days after dose. By 2 weeks after dose, inflammation levels in the bupivacaine HCl 0.5% group were lower than those in the other 2 treatment groups. No neurotoxicity was observed in any of the treatment groups. Another study, conducted by Richard et al,[24] assessed liposome bupivacaine 9, 18, and 30 mg/kg (1.33%) compared with bupivacaine HCl 9 mg/kg (0.75%) or placebo (normal saline) for brachial plexus block in rabbits and dogs. In this study, the investigators observed minimal to mild granulomatous inflammation of adipose tissue around nerve roots in

TABLE 6. Nervous System and Cardiac AEs Occurring in More Than 5% of Subjects in Any Treatment Group

System Organ Class	Liposome Bupivacaine <266 mg (n = 111)	Liposome Bupivacaine 266 mg (n = 210)	Liposome Bupivacaine >266 mg (n = 14)	Liposome Bupivacaine All Doses (n = 335)	Bupivacaine HCl (n = 33)	Placebo (n = 207)
Any nervous system disorder*	33 (30)	35 (17)	1 (7)	69 (21)	9 (27)	44 (21)
Hypesthesia	21 (19)	5 (2)	0	26 (8)	8 (24)	1 (0.5)
Dizziness	6 (5)	20 (10)	0	26 (8)	0	26 (13)
Headache	8 (7)	7 (3)	0	15 (5)	2 (6)	7 (3)
Paresthesia	6 (5)	1 (0.5)	0	7 (2)	4 (12)	0
Cluster headache	0	0	1 (7)	1 (0.3)	0	0
Any cardiac disorder*	4 (4)	24 (11)	3 (21)	31 (9)	0	24 (12)
Bradycardia	1 (1)	4 (2)	2 (14)	7 (2)	0	2 (1)
Sinus tachycardia	1 (1)	5 (2)	1 (7)	7 (2)	0	1 (0.5)

Values are reported as the number of subjects (percentage of treatment group).

*Subjects may have experienced more than 1 disorder in a particular system organ class.

brachial plexus sites of animals treated with liposome bupivacaine; they considered these effects to be a normal response to the liposomes and not adverse. Liposome bupivacaine was not associated with overt irritation, and no neurotoxicity was observed.

The most frequently reported AEs observed in the current analysis are consistent with the AE profile observed in previous studies of liposome bupivacaine administered at the surgical site.[14] Several of the most common AEs (nausea, constipation, and vomiting) observed in this analysis, as well as in the previously reported wound infiltration studies, could have been opioid related because use of rescue analgesia was permitted in all studies of liposome bupivacaine that included subjects undergoing a surgical procedure with postsurgical pain. It is also possible that some of the reported AEs could have been largely related to the surgical procedure itself. The incidences of AEs related to nervous system and cardiac disorders in the current analysis were also low and were similar in the liposome bupivacaine and placebo groups.

Previously, Viscusi and colleagues[14] evaluated the overall safety profile, and Bergese and colleagues[25] assessed the cardiac safety of liposome bupivacaine in analyses of pooled safety data from 992 subjects who received liposome bupivacaine infiltrated into a surgical site or healthy volunteers. Bergese and colleagues[25] reported that 3 subjects undergoing total knee arthroplasty had experienced excessive plasma bupivacaine concentrations: 8290 to 34,331 ng/mL compared with the group means of 255 to 520 ng/mL. The investigators suspected that these extremely high plasma concentrations resulted from unintentional intravascular administration of liposome bupivacaine. Importantly, none of these 3 subjects demonstrated any signs of central nervous system or cardiac toxicity, including ECG or QTc changes.

Bergese and colleagues[25] also reported 1 incident of tonic-clonic seizure in a healthy volunteer in a phase I study following subcutaneous injection of liposome bupivacaine 15 mg and bupivacaine HCl 2.5 mg in the right and left forearms, respectively. Before receiving any medication, the subject reported nausea followed by a vasovagal episode. Given that the 3 subjects with suspected intravascular injections of liposome bupivacaine exhibited plasma concentrations ranging from about 8000 to 34,000 ng/mL without experiencing any toxicity symptoms and the extremely low likelihood of accidental intravascular injection associated with subcutaneous injection, it is unlikely that this was truly a seizure and also unlikely that the event resulted from the liposome bupivacaine infiltration.

Limitations

Assessment of safety parameters was a secondary objective for all 6 of the studies included in this analysis; none of the studies were powered to detect between-group differences in AEs. Although randomized controlled clinical studies allow for rigorous assessment of the efficacy and safety of a given drug, the generalizability of results is limited because clinical study settings typically involve strict adherence to procedural protocols, specific inclusion/exclusion criteria, and rigorous follow-up procedures that are generally not possible in routine clinical care.[26] Postmarketing data based on approximately 600,000 patient exposures to liposome bupivacaine administered via wound infiltration suggest the AE rate following administration of liposome bupivacaine is less than 1% (data on file, unpublished results [Pacira Pharmaceuticals, Inc; 2014]). In addition, in the current analysis, subjects reported all events that occurred after the start of study drug administration, regardless of the association with liposome bupivacaine. As such, events that may be related to factors other than liposome bupivacaine, such as concomitant medications or underlying disease, were also captured. More studies are needed to evaluate the safety profile of liposome bupivacaine when used in different types of nerve blocks and in heterogeneous patient populations.

CONCLUSIONS

The available data from these 6 prospective and controlled clinical studies suggest that liposome bupivacaine may have a similar safety profile to bupivacaine HCl and normal saline. However, further studies are needed to better define the risk of AEs associated with this formulation administered as a peripheral nerve block. The authors emphasize that liposome bupivacaine is not currently indicated for use in peripheral nerve blocks and must be considered experimental at this time.

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APPENDIX: List of Investigational Review Boards

Study 1

Site-Specific Primary Investigators	IRB Name/Address
Tim Mant Charlie Brindley	Guy's Research Ethics Committee, 3rd Floor Nuffield House, Guy's Hospital, London, UK SE1 9RT

Study 2

Site-Specific Primary Investigators	IRB Name/Address
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Alexander Binning	West Ethics Committee, Administration Bldg, Ground Floor, Room 9, Western Infirmary, Dumbarton Rd, Glasgow G11 6NT
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Richard Langford	East London & The City LREC 3, 3rd Floor, Annuerin Bevan House, Aldgate, London E1 1RD
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Study 3

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Site-Specific Primary Investigators	IRB Name/Address
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Site 005 Harold Minkowitz	
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Site 009 Mark Hollmann	
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Site 020 Hayes Williams	
Site 022 Roger Setzler	
Site 025 Daniel Eloy	
Site 027 Stuart Styles	
Site 033 Joseph Gimbel	
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Study 6

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Site 201 Tanyo Stefanov	
Site 202 Alexander Tcherveniakov	
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(Continued)

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Site 401 Shota Gogishvili	Independent Ethics Committee of JSC "National Center for Tuberculosis and Lung Disease" 50 Maruashvili str., 0101 Tbilisi
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Site 501 Maciej Glogowski	
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Site 506 Hanna Misiolek	