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Delivery systems of local anesthetics in bone surgery: are they efficient and safe?

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Management of postoperative pain following bone surgery includes administration of local anesthetics (LAs). Smart delivery systems, including triggered systems, have been designed to provide a continuous release of LA *in situ*. However, these systems can provide a high level of LA locally. This review will examine the state-of-the-art regarding the LA delivery systems optimized for management of postoperative pain in bone surgery and will discuss the potential adverse effects of LAs on the overall pathways of bone healing, including the inflammation response phase, hemostasis phase, tissue repair phase and remodeling phase. There is a clinical need to document these effects and the potential impacts on the clinical outcome of the patient.

Introduction

Postoperative pain following bone surgery is a frequent concern. The severe pain caused by surgical interventions involving hard tissues can jeopardize treatment success, and compromise patient recovery, mobility, function, quality-of-life and autonomy, as well as prolonging hospitalization [1,2]. This postoperative pain can become chronic and therefore more difficult to manage. There is a potential connection between pain, inflammation and the healing process after bone surgery through the immune system. Consequently, pain management during the first four postoperative days should be as efficient as possible to minimize the risk of developing chronic pain and thus compromising the healing process.

Postoperative pain after bone surgery is usually managed with systemic administration of conventional analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids [3]. In addition to adverse effects induced by analgesics, their prescriptions increase the overall intervention costs, thus adding an economic burden on health system expenses [4]. In contrast to this systemic approach, local analgesia through peripheral nerve blocks is very promising because it can limit postoperative pain while avoiding complications and limitations of systemic drugs [5,6]. Unfortunately, therapeutic efficacy is largely compromised by a short effective duration. For this reason, delivery systems of local anesthetics (LAs) have been developed to achieve continuous analgesia.

Management of postoperative pain with local anesthetic drugs

Since the introduction of cocaine, various LAs have been adopted in clinical practice to manage postoperative pain [7,8]. Although binding to the sodium channel through the hydrophilic pathway is the main mechanism of action of LAs [9], alternative pathways described for uncharged LA (e.g., benzocaine) or, by contrast, for permanently charged LA (e.g., lidocaine derivative QX-314) also exist [10]. Uncharged LA can pass through the nerve membrane and reach the lateral fenestrations in the sodium channel. By contrast, influx of QX-314 seems facilitated by the formation of

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https://doi.org/10.1016/j.drudis.2018.06.019

Please cite this article in press as: Dupleichs, M. et al. , Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.06.019

TABLE 1

Physical, chemical and pharmacokinetic properties of the main LAs used in a clinical setting (amino-ester and amino-amide) [9]

		Physical-chemical			Pharmacokinetics				
		ionization constants (onset)	lipid solubility (potency)	protein binding (duration)					
	Drug	*pKa*	*O/B PQ*[a]	*PB %*	*MW (g/mol)*	*$t_{1/2}$ (h)*	*Clinical duration*	*Max. dose (mg/kg)*	*With Epi-*
Ester	Benzocaine				165				
	Cocaine	8.7 (slow)	(moderate)		303		0.5–1	3	?
	Chloroprocaine	8	(moderate)	(short)	271		0.5–1	11	14
	Procaine	8.9 (slow)	1.7 (weak)	6 (short)	236	0.1	0.5–1	12	?
	Tetracaine	8.5 (slow)	221	76	264		1.5–6	3	?
Amide	Articaine	7.8 (fast)	17 (moderate)	70 (short)	321	0.1		4	7
	Bupivacaine	8.1 (slow)	346 (potent)	95 (long)	288	3.5	1.5–8	2.5	3
	Lidocaine	7.9 (fast)	2.4 (moderate)?	64 (moderate)	234	1.6	0.75–1.5	4.5	7
	Mepivacaine	7.6 (fast)	21 (moderate)	77 (moderate)	246	1	1–2	4.5	7
	Prilocaine	7.9 (fast)	25 (weak)?	55 (moderate)	220	1.6	0.5–1	5–7	7–8.5
	Ropivacaine	8.1 (slow)	115 (potent)	94 (long)	274	1.9	1.5–8	3	3.5

Abbreviations: PB, protein binding; MW, mass weight.

[a] Partition coefficients were measured between oil and buffer (O/B) at pH 7.4 and 25 °C.

a large pore in response to stimulation of the transient receptor potential vanilloid 1. Table 1 summarizes physical–chemical and pharmacokinetic characteristics involved in the LA activity [9].

Unfortunately, therapeutic efficacy is largely compromised by a short duration of action (Table 1). To overcome this limitation, continuous and controlled administration of LA at surgical sites or around nerves that innervate the site is often used by surgeons. This local administration can extend analgesia to better prevent chronic pain with limited systemic effects. For example, femoral nerve block (FNB) has been shown to (i) reduce the postoperative need for opioids after total knee arthroplasty (TKA), (ii) reduce hospital stays of patients and (iii) increase ability to undergo physical therapy compared with patients receiving oral analgesia postoperatively. However, this technique can be associated with a risk of decreased muscle tone of the quadriceps, which counteracts effective rehabilitation and increases the risk of patient falls [11]. Local infiltration analgesia (LIA) is an alternative regional anesthesia method for the control of acute postoperative pain following knee and hip replacement surgery. Patients who received local periarticular injection of ropivacaine, ketorolac and epinephrine showed lower pain levels as compared with those who received FNB [12].

Despite these clinical benefits, the efficacy of LAs is still limited by the short duration of analgesia. With a view to prolonging LA duration without compromising patient safety, different options have been envisaged including drug delivery systems, structural modification of LA molecules and coadministration of vasoconstrictors. Among them, prolonged-release formulations of LA using biocompatible drug carriers (Table 2) have been designed to remain at the site of injection and release LA slowly over time at a therapeutic dose. These systems should be easily and simply administered to patients.

TABLE 2

Description of characteristics required for a LA delivery system

Clinical efficacy	Protection of local anesthetic (LA)
	Solubilization of LA
	Sustained release of LA
	Prolonged duration of nerve block
	Favorable ratio of sensory and motor blocks
Safety	Biocompatible
	Biodegradable
	Avoiding high local level of LA
	Minimal local inflammation response
	Absence of neurotoxicity
	Absence of myotoxicity
	No systemic toxicity
	Stability of formulation
Administration formalities	Easy to administer to patients
	Initiated by a single administration
	No need of general anesthesia or surgical procedure
	No need of sophisticated materials
Manufacturing process	Cost effective
	Easy to produce
	Industrial scale-up

Formulation for optimized delivery of local anesthetics

Polymers

Hydrophobic polymers such as poly(lactic-co-glycolic acid) (PLGA) and PEG–polylactic acid (PELA) have been used to produce particles for controlled release of LA. Release profile can be optimized by varying the size of particles, drug content, polymer:drug ratio and excipient used. Administration of PLGA microspheres significantly prolongs the release of bupivacaine to 144 h, whereas plasma levels of bupivacaine were undetected 8 h after injection of bupivacaine solution [13]. Qi *et al.* [14] investigated the analgesic effect of ropivacaine–PELA nanoparticles (10% w/w) on a postoperative pain model in rats. These nanoparticles increased the duration of sciatic nerve block over 3 days after a single administration, whereas systemic injection of ropivacaine was only effective for 8 h. This prolonged release could result in long-lasting local exposure of the nerve to ropivacaine with the metabolism of the PELA nanoparticles.

Recently, lipid–polymer hybrid nanoparticles (LPNs) have also been used to regulate the release of bupivacaine [15]. LPNs consist of two major components: (i) the PLGA core capable of encapsulating hydrophilic and hydrophobic drugs; and (ii) single or multiple lipid

Please cite this article in press as: Dupleichs, M. et al. , Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.06.019

layers (lecithin). By combining the characteristics of polymeric nanoparticles and lipids, LPNs provide high structural integrity, stability during storage and prevent the fast release of the drugs. Indeed, prolonged controlled release of bupivacaine from LPNs was observed for up to 96 h with only 19.3 ± 3.6% of the drug released at 10 h compared with 50.7 ± 3.1% of release at 10 h obtained with bupivacaine-loaded PLGA nanoparticles. Electrical stimulation on mice showed these LPNs increased the duration of analgesia by 5 h compared with bupivacaine-loaded PLGA nanoparticles.

Interestingly, chitosan (CS) has been included in LPN formulations to create a strong crosslinking complex of CS resulting in denser particles that can delay lidocaine release [16]. As expected, its release was slower than that of the liposomal formulation. The release profile exhibits a biphasic pattern characterized by an initial burst-release of ~40% of the lidocaine in 8 h followed by sustained release up to 72 h (vs 48 h for liposomes). This slower release of lidocaine results from its entrapment by the lipid matrix.

Liposomes

A liposomal bupivacaine formulation (Exparel®) was recently approved by the FDA in 2011 for postsurgical analgesia. Briefly, this multivesicular liposome contains a novel phospholipid excipient, dierucoylphosphatidylcholine, cholesterol and tricaprylin, which allows a particularly high capacity for bupivacaine loading (fivefold ratio compared with conventional preparations). After its injection into trochanter in rats, sciatic nerve block lasted 240 min as compared with 120 min for 0.5% (w/v) bupivacaine HCl and 210 min for 1.31% (w/v) bupivacaine HCl [17]. A Phase II dose-ranging study on patients with TKA reported that a 532 mg dose extended the duration of local analgesia from under 12 h to 5 days. This therapeutic dose was well-tolerated, had a higher safety margin and showed a favorable safety profile compared with bupivacaine and control groups [18].

To date, several randomized clinical trials have shown that liposome bupivacaine periarticular injection can provide better postoperative analgesia compared with placebo or plain bupivacaine by periarticular injection or nerve block [19,20]. Liposome bupivacaine can reduce pain score and opioid analgesia consumption and shorten hospitalization in patients who underwent TKA [21]. It might be able to improve postoperative physical performance of walking and stairclimbing, to reduce hospitalization cost and speed up postoperative recovery in TKA [22]. Recently, co-injection of liposomal bupivacaine with a co-delivery of two encapsulated adjuvant compounds, dexamethasone and dexmedetomidine, has been shown to enhance the duration of sciatic nerve block 2.9-times more than liposomal bupivacaine alone [23].

Currently, published data are still insufficient to establish a well-conducted comparison between liposome bupivacaine and various mixtures of non-opioid analgesia. Indeed, there is not enough evidence to support whether liposome bupivacaine is superior to a standard analgesic mixture, considering the aspects of pain relief, opioid consumption and hospital stay. Although liposomes have excellent properties for drug delivery, their use remains compromised by physical instabilities (size increase by vesicle fusion) and chemical instabilities (lipid peroxidation) during storage limiting their shelf life, sterilization and industrial scale-up.

Calcium phosphate bone substitutes

Calcium phosphate (CaP) biomaterials are extensively used for bone reconstructive surgery because they are biocompatible, bioactive and osteoconductive [24]. Interestingly, they can act as local drug delivery systems [25,26]. The first combination of CaP with bupivacaine provided a dose-dependent analgesic effect during the first postoperative days [27]. Lidocaine has been mixed with different kinds of CaP cement (CPC) components. The drug release depends on cement pH and composition and can be prolonged for up to 6 days [28]. Salts of lidocaine, bupivacaine and levobupivacaine were incorporated into the solid phase of CPC [29]. Cement released >60% of the lidocaine within the first 24 h, whereas bupivaine or levobupivacaine reached 60% release after 144 h of incubation. Recently, a critical-size bone defect of rat femur was filled by an injectable CPC loaded with bupivacaine or ropivacaine [30]. The functional evaluation of the gait performed with the CatWalk system demonstrated significant pain relief during the short-term postoperative period.

Smart controlled systems

In the era of personalized medicine, LA delivery systems should achieve responsive and adjustable release according to the changing needs of patients in terms of timing, intensity and duration of analgesia. In this attempt, three leading-edge external triggers have been conceived based on light, ultrasound and magnetic fields and could be placed on a nerve allowing the patient to achieve precise titration of LA [31]. Because tissue penetration by light is dependent on its wavelength and power, relatively deep light penetration of tissue should be expected at near infrared (NIR) wavelengths (650–900 nm) up to 10 cm. Following irradiation, gold nanorods (GNRs) incorporated within liposomes can convert light energy to heat resulting in a phase transition of the lipid bilayer or pressure fluctuations that disrupt the lipid membrane. Subsequently, the ordered gel phase is transformed into a disordered liquid crystalline phase allowing the release of LA contained within the liposomes. After their implantation into a rat hind paw, irradiation with NIR light (808 nm) induced repeated infiltration analgesia [32]. Interestingly, varying the irradiance and duration of irradiation can modulate the analgesic effect. However, NIR light can be significantly attenuated with progressive depth and increasing irradiance can induce severe tissue injury. Consequently, the formulation has been modified to render liposomes more sensitive to low temperatures [33]. In fact, this new formulation was sensitive to low irradiance over short durations (1–2 min), which would be ideal to relieve pain as quickly as possible.

A photosensitizer contained inside liposomes produced singlet oxygen upon irradiation with NIR light resulting in peroxidation of unsaturated lipids in the liposome bilayer. Consequently, liposomes became more permeable and released encapsulated LA [34]. *In vitro* release of LA reached ~6% in response to NIR irradiation. Injection of these liposomes at the sciatic nerve of rats provided an initial nerve block lasting 13.5 ± 3.1 h. Repeated periods of nerve block could be induced by NIR irradiation. The effective sensitivity to light of devices has been enhanced by co-delivering dexmedetomidine [31]. As an α2-adrenergic agonist, dexmedetomidine induced local vasoconstriction maintaining a high local concentration of co-administered LA. Dexmedetomidine provided effective triggering

Please cite this article in press as: Dupleichs, M. et al. , Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.06.019

with irradiation at 75 mW/cm^2 over 5 min compared with 330 mW/cm^2 over 15 min without dexmedetomidine. Moreover, the threshold for providing nerve block was reduced from 76 J/cm^2 to 4 J/cm^2 with dexmedetomidine. Finally, dexmedetomidine enhanced the therapeutic effect of the released LA resulting in more nerve block events triggered (9 vs 2 without dexmedetomidine).

Unlike light, ultrasound is a common noninvasive technique that can be applied in a focused manner minimizing energy in surrounding tissue. Using parameters similar to those used in clinical imaging (high-frequency low-intensity ultrasound; HFLIU) seems to be safe [35,36]. Many of the current ultrasound-triggerable drug delivery systems, such as micelles, liposomes, composites and hybrid materials, are responsive to the thermal and mechanical effects of ultrasound waves. Recently, smart liposomes containing sonosensitizer protoporphyrin IX have been shown to release reactive oxygen species (ROS) in response to ultrasound stimuli. Once released, ROS peroxidated the unsaturated lipids in the bilayers leading to the release of LA. For example, liposomes provided ~36 h of continuous initial nerve block on a rat sciatic nerve model [37]. The nerve block duration depends on the extent and intensity of insonation. It would then allow an additional half-day off on-demand nerve block, enabling personalized narcotic-free pain management.

Based on previous studies demonstrating the efficiency of exogenous microbubbles to enhance drug flow through the skin [38], Cullion *et al.* have explored the positive effects of HFLIU in conjunction with microbubbles on two LA-mediated nerve blocks (i.e., tetrodotoxin and bupivacaine) [39,40]. Their device markedly improved LA block frequency and duration of sensory and motor nerve block. For example, 25 μM tetrodotoxin in combination with HFLIU and microbubble treatment resulted in reliable nerve block, and 30 μM tetrodotoxin induced a nerve block greater than or equal to the duration achieved with 0.5% bupivacaine.

To summarize, these innovative triggerable drug delivery systems should achieve adjustable on-demand local anesthesia in terms of dose magnitude and timing. The dynamic range of release kinetics can be adjusted by changing the composition and geometry of the membrane to match the therapeutic window for optimized analgesia. However, efforts must be continued to provide excellent reproducibility and low off-state leakage. Once optimized, these devices based on continuous-wave laser systems or LEDs would be perfectly adapted for point-of-care systems, reducing the costs of health systems. Table 3 shows the main results obtained from biological studies.

Biological drawbacks of high levels of LA

Regardless of the method or delivery system used, local release of high levels of LA could impact the short-time wound healing process. This could partially be the result of the deregulation of the initial inflammatory response and later tissue proliferation. The overall pathways of bone healing include inflammation response phase, hemostasis phase, tissue repair phase and remodeling phase. Consequently, there is a clinical need to document these effects and the potential impacts on the clinical outcome of patients.

Inflammatory response

LAs have been described to have anti-inflammatory properties during the main stages of bone healing (i.e., homeostasis, inflammation, proliferation, differentiation). Despite the fact that the molecular mechanism of their anti-inflammatory effect remains unclear, several hypotheses have been proposed. For example, perioperative immunosuppression observed in surgical patients, as well as the proinflammatory and anti-inflammatory cytokines, synergistically increases its suppressive effects on the immune system [41]. Also, LAs could modulate various steps of the inflammatory cascade including leukocyte adhesion, migration, activation and granulocyte phagocytosis. Furthermore, LAs have been shown to affect polymorphonuclear neutrophils (PMNs) directly, as well as macrophage and monocyte function in a dose-dependent and reversible manner [42]. Ropivacaine and lidocaine (100–300 mM) decreased tumor necrosis factor (TNF)-α-induced upregulation of CD11b/CD18 surface expression on PMNs *in vitro*, thus leading to a decrease of PMN adherence, migration and accumulation at the site of inflammation [41].

Local tissue reactivity has also been assessed after injection of liposomes containing LA. Animals receiving liposomes showed mild inflammation at the injection site. Foamy macrophages were observed at the injection site, showing particle uptake [31]. The mild inflammation from liposome injections is generally considered safe [20,43]. Recently, safety concerns relating to the new generation of triggered drug delivery systems have been addressed. For example, insonation caused no significant inflammation when ultrasound parameters were similar to those used for therapeutic ultrasounds [37].

Tissue injury

In vitro LAs have shown cytotoxic effects on muscular cells [44], fibroblast cell lines [45] and intervertebral disc cells [46]. This could undermine neovascularization, fibroblast proliferation and collagen secretion, and could downregulate the proliferative stage of wound healing. Bupivacaine caused more myotoxic damage than levobupivacaine and ropivacaine in the skeletal muscle of rats [44].

Animals injected with liposomes loaded with LA showed mild inflammation at the injection site, whereas minimal inflammation was seen in the adjacent muscle [31] and no significant tissue toxicity was reported from liposomes [20]. Moreover, special attention should be paid to the latest generation of triggered drug delivery systems. For example, animals treated with 1 MHz ultrasound for 5 min at an acoustic intensity of 0.1 W/cm^2 had mild residual inflammation at 14 days and myotoxicity had resolved by 14 days [40]. Similarly, there was no tissue toxicity either immediately after applying ultrasound at 3 W/cm^2, 1 MHz, 10 min or in the following four days [37]. Because ultrasound can have intrinsic effects on neuronal function, neurotoxicity of these triggered systems has also been evaluated. Previous studies using animal models of neuronal injury demonstrated that neuronal suppression secondary to acoustic waves is proportional to acoustic intensity administered, with focused high intensity (35 W/cm^2) resulting in suppressed axonal conduction. Intensities of 390–3000 W/cm^2 generating nerve block that lasts for weeks, and very high intensity (7890 W/cm^2) causes almost complete axon degeneration [47]. Fortunately, these intensities are orders of magnitude higher than those required by these triggered delivery systems. At lower ultrasound intensities, ultrasound induces nerve stimulation rather than suppression. Applying HFLUI did not induce nerve damage during a 2-week observation period following injec-

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TABLE 3

Summary of data obtained from *in vitro* and *in vivo* evaluations of LA delivery systems

***In vitro* studies**

Authors	*Year*	*Materials*	*Formulation*	*Loaded LA*	*Duration of release*	*Refs*
Ma *et al.*	2017	PLGA hybrid	Nanoparticles	Bupivacaine	96 h	[15]
Wang *et al.*	2016	Lipid–polymer hybrid	Nanoparticles	Lidocaine	72 h	[16]
Wang *et al.*	2016	PELA	Nanoparticles	Ropivacaine	3 days	[16]
Verron *et al.*	2010	CaP	Microgranules	Bupivacaine	24 h	[27]
Irbe *et al.*	2012	CaP	Cement	Lidocaine	6 days	[28]
Colpo *et al.*	2018	CaP	Cement	Bupivacaine Levobupivacaine	60% at 144 h	[29]
Dupleichs *et al.*	2018	CaP	Cement	Bupivacaine Ropivacaine	72% at 96 h 64% at 96 h	[30]
Rwei *et al.*	2017	Sonosensitizer	Liposome	Tetrodotoxin	7% at 2 h	[31]
Zhan *et al.*	2016	Gold nanorod	Liposome	Tetrodotoxin	10% at 10 min	[32]
Zhan *et al.*	2017	Gold nanorod	Liposome	Tetrodotoxin	2–19% irradiation	[33]
Rwei *et al.*	2015	Photosensitizer	Liposome	Tetrodotoxin	5.6% at 2 h	[34]

***In vivo* studies**

Authors	*Year*	*Materials*	*Formulation*	*Loaded LA*	*Duration of anesthetic effect*	*Refs*
Schmidt *et al.*	2015	PLGA	Microsphere	Bupivacaine	144 h	[13]
Qi *et al.*	2016	PELA	Nanoparticles	Ropivacaine	3 days	[14]
McAlvin *et al.*	2014	PLGA	Liposome	Bupivacaine	240 min	[17]
Rwei *et al.*	2018	Lipid mixture	Liposome	Bupivacaine	16 h	[23]
Verron *et al.*	2010	CaP	Microgranules	Bupivacaine	72 h	[27]
Dupleichs *et al.*	2018	CaP	Cement	Bupivacaine Ropivacaine	>72 h >72 h	[30]
Rwei *et al.*	2017	Sonosensitizer	Liposome	Tetrodotoxin	36 h	[31]
Zhan *et al.*	2016	Gold nanorod	Liposome	Tetrodotoxin	5 h	[32]
Zhan *et al.*	2017	Gold nanorod	Liposome	Tetrodotoxin	62 h	[33]
Rwei *et al.*	2015	Photosensitizer	Liposome	Tetrodotoxin	24 h	[34]
Cullion *et al.*	2018	Lipid mixture sonication	Microbubbles	Tetrodotoxin	134 min	[40]

Abbreviation: LA, local anesthetic.

tion [40]. Similarly, no significant neurotoxicity was observed in any animals receiving ultrasounds at high frequency (1 MHz, 3 W/cm^2) [37].

Hemostasis

Although it is well-known that LA infiltration causes vasoconstriction at low concentrations and vasodilation at high concentrations, the vasoactive effect varies depending on the drug used, because the latter determines either vasoconstriction or vasodilation. For example, prilocaine and mepivacaine are rather vasoconstrictory at clinical doses whereas lidocaine has vasodilator activity. Of the two enantiomers of bupivacaine, the S(−)levorotatory one seems the most vasoconstrictive. However, changes in the pulpal blood flow measured in patients treated with 0.5% levobupivacaine or 0.5% bupivacaine are not statistically different [48].

Also, vasoconstrictor molecules have usually been added to LA to effectively reduce drug absorption and toxicity, as well as surgical bleeding. Although a recent RCT found that, after total hip arthroplasty, LA with epinephrine infiltration did not significantly modify pre- and post-operative bleeding [49], LA infiltration has been shown to reduce bleeding after TKA. Hemostasis changes have been extensively studied following injections of various LAs ± epinephrine in patients undergoing dentistry surgery such as tooth extractions [50–52]. Data strongly suggest an absence of significant hemodynamic modifications regardless of the administration protocol used (concentration of LA, ratio of LA:epinephrin). Nevertheless, further studies are still needed to address the related mechanisms affected by LAs to understand the mechanism of vasodilative and vasoconstrictive effects.

Osteoarticular regeneration

Effects of LAs on mesenchymal stem cell (MSC) activity have been studied because they can differentiate into a variety of cell types, including osteoblasts, chondrocytes, myocytes and adipocytes. MSCs probably play a crucial part in healing following surgical procedures such as microfracture and ligament reconstruction. Ropivacaine caused the fewest adverse effects on human MSCs, whereas lidocaine or bupivacaine seem to induce the most significant effects on MSC viability [53]. Herencia *et al*. investigated the role of procaine in osteo/odontogenesis of rat bone marrow MSCs *in vivo* [54]. They observed that procaine administration drastically

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reduces the mineralization and osteo/odontogenesis of bone marrow MSCs by inhibiting the Wnt/β-catenin pathway through the increase of Gsk3β expression and β-catenin phosphorylation. These effects of procaine were also observed on mature osteoblasts.

Chondrolysis is the irreversible destruction of previously normal articular cartilage, including the matrix and cellular element. Intra-articular injection of LAs increased risk of chondrolysis for patients after articular surgeries [55]. However, potential associations, including high-flow intra-articular pain pumps, thermal devices, type of anchors and various sutures must be taken in consideration. A causal relationship between the infusion of LAs and the development of glenohumeral chondrolysis has been established [56]. Results showed bupivacaine, lidocaine, ropivacaine and levobupivacaine are all toxic to cartilage in a dose-dependent manner. In summary, although these devices are biocompatible, potential biological drawbacks as a result of high local levels of LAs highlight the need to control and optimize the release of LAs from the delivery systems.

Concluding remarks and future perspectives

Multimodal management of postoperative pain is based on the administration of LAs. One of the major challenges is to design a biocompatible and resorbable biomaterial capable of delivering LAs continuously at therapeutic doses *in situ* without damaging the surrounding soft tissues (Table 2). Even though the clinical efficacy of such smart delivery systems might be of high benefit in pain management, an objective comparison of results from different studies remains difficult owing to the various protocols and formulations used. Furthermore, interpretation of *in vivo* data is extremely complex because it depends on the animal model, the nerve blocks tested and the pain assessment methods. Indeed, pain assessment is obviously operator- and animal-model-dependent. Standard and validated international guidelines in the spirit of International Conference Harmonization guidelines for drug approvals would be extremely helpful for comparing all these delivery systems. The absence of standardized methods could explain why only a few formulations are the subject of ongoing clinical trials or on the market.

Inflammation, neurotoxicity and myotoxicity are of the greatest concern and seem to be related to high local concentrations of LAs. Although several studies in the literature reported the absence of adverse cellular and tissue responses, it seems premature to conclude on the safety of high local levels of LA. In addition, recent methods of stimulation based on light or ultrasound could interfere and undermine the bone healing process. Finally, local production of ROS must be tightly regulated because ROS will dramatically affect bone cell health and thus bone regeneration. All these concerns need to be extensively investigated in further studies to recommend the clinical use of these delivery systems for the entire population.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding this review.

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Please cite this article in press as: Dupleichs, M. et al. , Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.06.019

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Please cite this article in press as: Dupleichs, M. et al. , Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.06.019