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Review Article

Liposomal bupivacaine – New trends in Anesthesia and Intensive Care Units

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Abstract Progress made on local anesthetics controlled release formulation and their ability to induce motor and sensory block for a longer period of time brings significant advantages in clinical practice. The use of sustained release formulations provides analgesia for a long period of time with one administration, thus limiting the complications that can occur with conventional analgesia. Also, controlled release of a biologically active compound prevents overdosing, minimizing the side effects, especially cardiotoxicity, neurotoxicity and tissue lesions. Clinical use of liposomal formulation brings high impressive results in pain control and quick patient recovery. Increased patient comfort, reducing to half the hospital length of stay, and treatment costs are able to provide a higher level of healthcare.

Contents

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1. Introduction

Pain management represents one of the major therapeutical goals in Intensive Care Unit [1,2]. Opioids represent the gold standard in pain control [3]. However, their systemic administration is associated with unwanted and potentially severe side effects [4] such as respiratory depression, drowsiness and sedation, nausea and vomiting, allergies and neutrophil disfunction [1–7].

Therefore, many sustained release systems were studied using local anesthetic agents [8], liposomal bupivacaine being the most studied system [9]. The present paper presents different liposomal systems used to obtain analgesia, and their applications in Anesthesia and Intensive Care Unit.

2. Liposomal drug delivery systems

Liposomes are spherical, small dimension nanovesicles consisting in a phospholipidical double layer [10,11]. Phospholipids have a polar group and two hydrophobic groups, usually an unsaturated fatty acid. Because in their constitution there is also a hydrophilic part, a number of water soluble active substances can be encapsulated without the drug structure being affected [12,13].

Currently, liposomes are of particular interest in clinical treatment due to its important properties (Fig. 1). Among these, the cell membrane biocompatibility and the ability to graft different ligands on their surface are the most important [10,14]. For this purpose, various controlled release systems based on liposomal nanovesicles have been developed. Several obstacles in drug release have been observed, mainly due to the interaction of the nanovesicles with high density lipoproteins in blood [15,16]. To minimize side reactions that lead to decreased efficacy of liposomal systems, nanovesicles were biofunctionalized with various compounds, increasing their bioavailability and reducing their absorption by the reticuloendothelial system [12,16].

2.1. Biofunctionalized polymeric liposomal system

Biofunctionalizing the liposomes with polyethylene glycol (PEG) (Fig. 2) [15] prevents the interaction between the liposomal nanovesicles and the mononuclear phagocytic system [12,17], obtaining a higher pharmacokinetic response. Li et al. [16] have evaluated the influence of polyethylene glycol (PEG) upon the time that the nanovesicles are retained in the blood. They evaluated LPD complex (liposome-polycation-DNA) [16] which was synthesized using cationic liposome, nucleic acids and protamine [16]. Experimental results highlight that by functionalizing liposomal vesicles with PEG, the pharmacodynamic properties of liposomal systems increase and their inactivation is minimized.

Ying Li and collaborators have investigated the consequences of biofunctionalized controlled release systems composed of liposomal bufalin and pectin [11]. Bufalin [19] represents a chemotherapeutic agent mainly used for colon cancer and gastric cancer [18]. Bufalin administration entails a number of negative effects due to increased toxicity of the active substance and low solubility in water. Thus, it has been administrated in the liposomal form in order to reduce the overconcentration in the body and increase the therapeutical effect. In their study, liposomal bufalin has been functionalized with citrus pectin (Fig. 3) – a non-toxic polymer, biodegradable and biocompatible in order to increase the stability of the liposomal complex [11]. Analyses have shown the benefits of biofunctionalization with a biocompatible polymer upon liposomal controlled release systems [11] (Fig. 4).

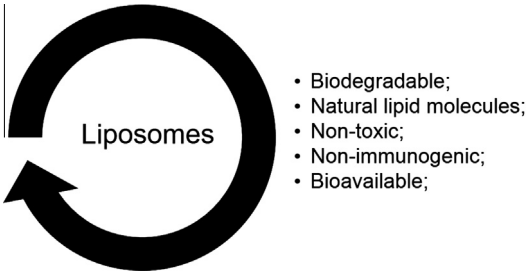

Figure 1 Properties of liposomal nanovesicles.

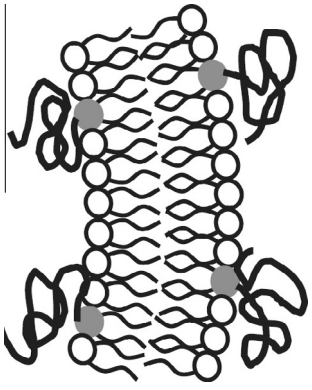

Figure 2 PEGylated lipid bilayer [15].

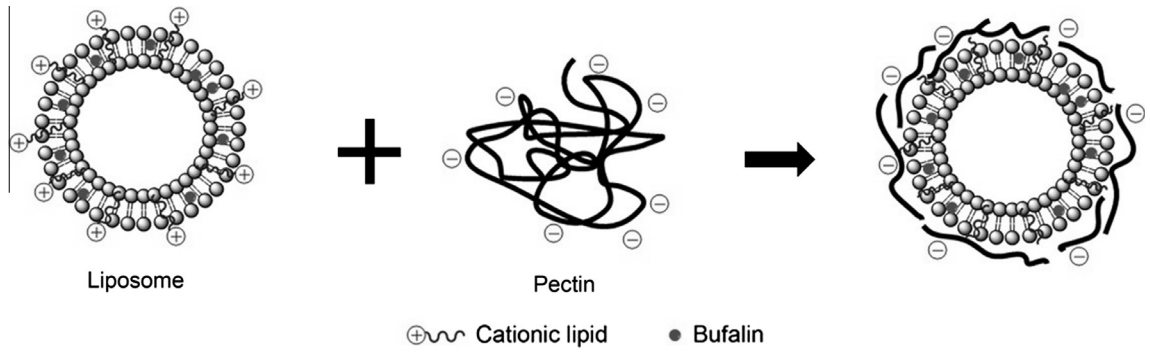

Figure 3 Liposomal bufalin functionalized with citrus pectin [11].

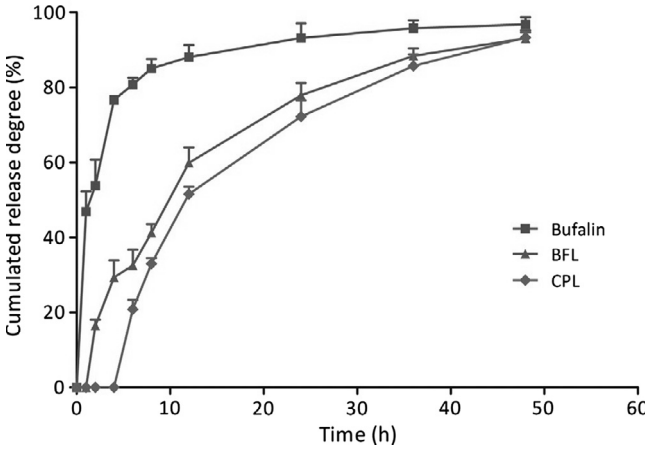

Figure 4 In vitro release kinetic profiles of bufalin from liposomal bufalin (BFL), liposomal bufalin functionalized with pectin citrus (CPL) compared to freely soluble bufalin [11].

3. Bupivacaine – structure, mechanism of action, toxicity

3.1. Chemical structure

Bupivacaine is a synthesis derivate, with chemical configuration similar to the first local anesthetic ever discovered – cocaine [20–22]. For a local anesthetic agent to be useful, it must have some characteristics: increased potency, sufficient duration of action, low systemic toxicity, low local toxicity, short onset time, high solubility in water, easily sterilizing [20,23,24]. The chemical structure of bupivacaine (see Fig. 5), highlights different subunits: an aromatic group, an intermediate chain which includes an amide link and an amine group. The liposolubility is due to the aromatic ring, allowing the compound to cross the axonal membrane, essential step in anesthetic action.

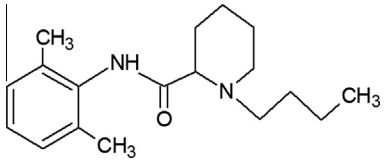

Figure 5 Bupivacaine – chemical structure.

Anesthetic liposolubility generates its intrinsic potency and the onset time. Hydrolysis takes place in the amide bond, the degradation is mainly in the liver and the degradation compounds rarely induce allergic reactions [20,25,26]. An increase in molecular volume increases the anesthetic potency to a certain level when it starts to decline. Finally, we can say that the chemical structure influences anesthetic liposolubility, water solubility, pharmacokinetics and eventually block characteristics and clinical effects [27].

3.2. Mechanism of action

Neuronal membrane is characterized by a resting potential generated by electric potential difference (60–90 mV) between the internal and external membrane [28]. The resting membrane is impermeable to Na^+ and there is a concentration gradient between intracellular and extracellular environment (14 mmol/L and 142 mmol/L) [29]. The depolarizing process is carried out by electrical charge transfer from outside to inside of the cell membrane until the reversal of the potential at which time the Na^+ channels are closed [30]. In the process of repolarization K^+ ions move out of the cell to restore the resting membrane potential [21]. Local anesthetics act after diffusion through the nerve sheath and axonal membrane, conversion to ionized form, binding of the ionized molecule to the Na^+ channel, blocking the flow of Na^+ ions inside the cell, therefore blocking the neuronal membrane depolarization and preventing the spread of the electrical impulse throughout the nerve [31,32]. The main characteristic of the anesthetic agents is the ability to exist in solution, in both unionized and ionized forms [33]. The neutral form is less water soluble, but highly liposoluble which favors crossing the lipidic cell membranes [34–37].

The ionized form is less liposoluble but strong watersoluble, which allows binding to specific receptors on the Na^+ channel and determining closing the channels which stops the Na^+ flow and prevents nerve fiber depolarization [23,26–28].

3.3. Toxicity of local anesthetics

Systemic toxicity is caused by high concentrations of local anesthetics. They occur accidentally by injection directly into the systemic circulation or by overdose [38]. Most sensitive to the toxic action of local anesthetic agents are central nervous system [39] and cardiovascular system [40,41]. Therefore

the symptoms can include isolated muscle contractures, incoherent speech, generalized convulsions, loss of consciousness [42], coma and respiratory depression [43,44].

Cardiovascular changes include tachycardia, slight increase in arterial tension, followed by PR and QRS prolongation [27,41]. AV block or various arrhythmias, decreased cardiac output and accentuated hypotension and ultimately asystole or ventricular fibrillation [34]. Studies have shown that bupivacaine has a higher affinity for cardiac tissue than lidocaine, thus cardiovascular collapse occurs faster. Cai et al. [1] have shown in their study that bupivacaine, tetracaine and etidocaine have a higher tendency to impair the cardiovascular system or depress the central nervous system compared with lidocaine, mepivacaine and prilocaine [1]. The main obstacle in using bupivacaine is pronounced systemic toxicity [45,46].

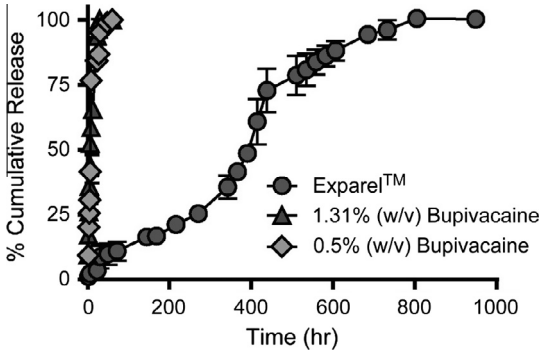

Figure 6 Cumulative release of bupivacaine form Exparel™ and release of unencapsulated 1.31% w/v and 0.5% w/v bupivacaine HCl [57].

The toxic concentrations initially cause marked sympathetic stimulation, but later myocardial contractility depression and ventricular arrhythmias carrying the risk of nonresuscitable cardiac arrest [47]. ECG analysis reveals in early stages PR prolongation and QRS widening followed by the appearance of malign arrhythmias [31]. Due to its increased liposolubility and protein binding (heart muscle binding is rapid, but elimination is slow), bupivacaine-induced cardiac arrest is impossible in clinical practice. Pregnant women [48] are susceptible to cardiotoxicity due to the fact that cardiac depression is increased by progesterone [49–51]. In order to limit the toxic consequences of bupivacaine and provide a favorable effect in clinical practice, alternatives have been developed for controlled release of the active substance in order to support the motor and sensory local block for a longer period of time, thus enhancing patient safety.

For this purpose, a number of biomaterials are being studied: lipospheres, microspheres [52], cyclodextrin matrices, lipid–protein–sugar nanoparticles, microcrystals, implantable pellets, implantable membranes and, not least liposomal bupivacaine [53–57].

4. Liposomal bupivacaine

Liposomal bupivacaine has recently been introduced in clinical practice [56,57] and is tested in many clinical studies on healthy volunteers in order to obtain long-lasting pain relief in a single dose administration (DepoFoam bupivacaine, Exparel™) [53]. Liposomal bupivacaine consists of liposomal spheres with diameter between 31.2 μm ± 17.8 [53]. In vitro studies regarding controlled release system compared the Exparel™ complex with bupivacaine hydrochloride 0.5% (w/v) and 1.31%

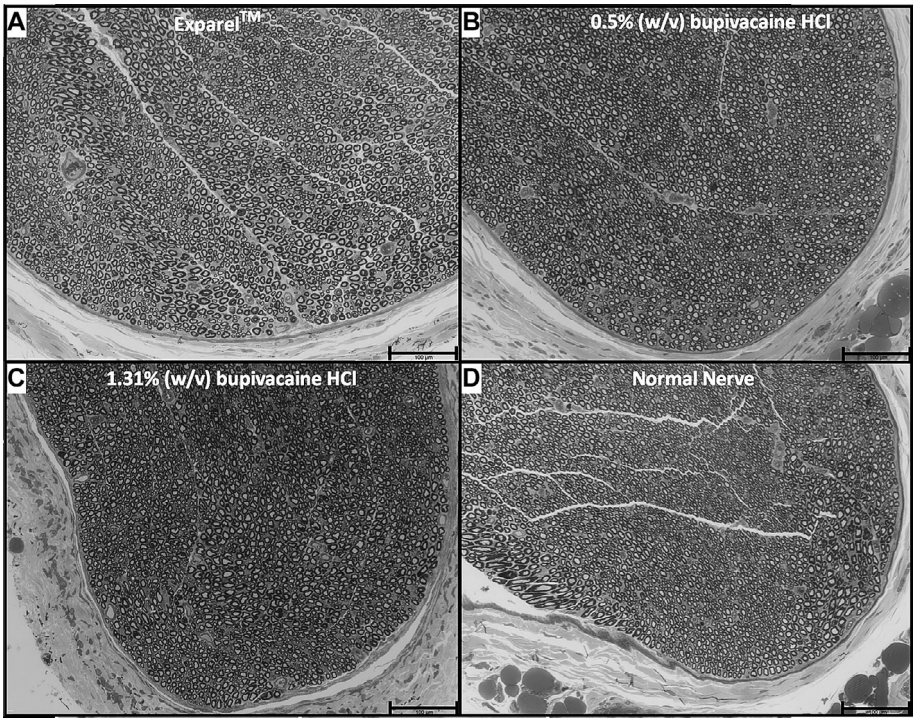

Figure 7 Sciatic nerve samples harvested from rats 4 day after injection with either Exparel™ (A), bupivacaine HCl 0.5% w/v (B), bupivacaine HCl 1.31% w/v (C) or uninjected sciatic nerve (D) [57].

respectively, with an equal amount of active substance. Release kinetics profile was identical in the case of hydrochloride from free bupivacaine with a maximum time release of 48 h, while regarding the Exparel™ complex [53,57], the active substance has been fully released in about 800 h (Fig. 6).

McAlvin et al. [57] studied the effect of liposomal bupivacaine on the sciatic nerve in experimental models, and obtained sensory block for 240 min for the Exparel™ complex and 120 min for bupivacaine hydrochloride 0.5% (w/w) [57]. After histological evaluation, they found that both Exparel complex and bupivacaine hydrochloride produce tissue reaction, the liposomal complex being less aggressive. The degree of mycotoxicity was similar in both pharmaceutical preparations, which was examined 2 weeks after administration. Also, the perineural tissue appears normal, without emphasizing significant changes in axonal density and myelin structure [57] (Fig. 7).

Lonner et al. [58] studied the role of liposomal bupivacaine in pain management after total joint arthroplasty, and observed that liposomal bupivacaine pharmacokinetics and pharmacodynamics are supporting a minimum concentration necessary to maintain the therapeutical effect for 72 h without overconcentrating the active substance in the body [58]. Thus, liposomal bupivacaine has less cardiac toxic effects, without significant differences between Exparel™ and placebo: palpations and extrasystoles (⩽2%) [58], tachycardia (3.9%) [58], bradycardia (1.6%) [58], hypertension and hypotension (⩽2%) [58].

Richard et al. [59] showed no significant hematological, biochemical and biological side effects of Exparel complex in laboratory animals. Histological analysis 15 days after administrating Exparel™ formulation showed evidence of granulomatous inflammation that was resolved without significant tissue damage. The optimum plasma concentration was maintained for about 96 h [59]. Liposomal bupivacaine used in postoperative patients reduces the need for opioids, the hospitalization period and costs by up to 50%, as shown by Cohen [60] and collaborators in clinical trials involving sigmoidectomy, cecectomy, hemicolectomy (right or left) in adult patients [60].

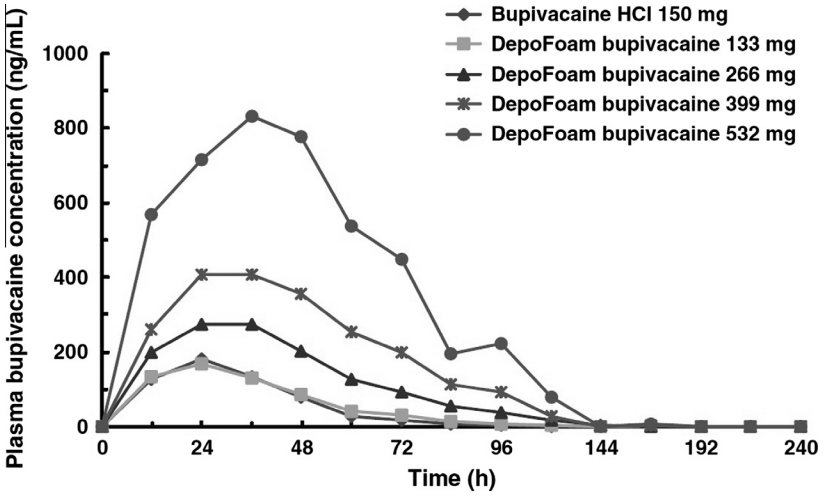

Figure 8 Plasma bupivacaine concentration after administration of DepoFoam bupivacaine or bupivacaine HCl to patients undergoing total knee arthroplasty [62].

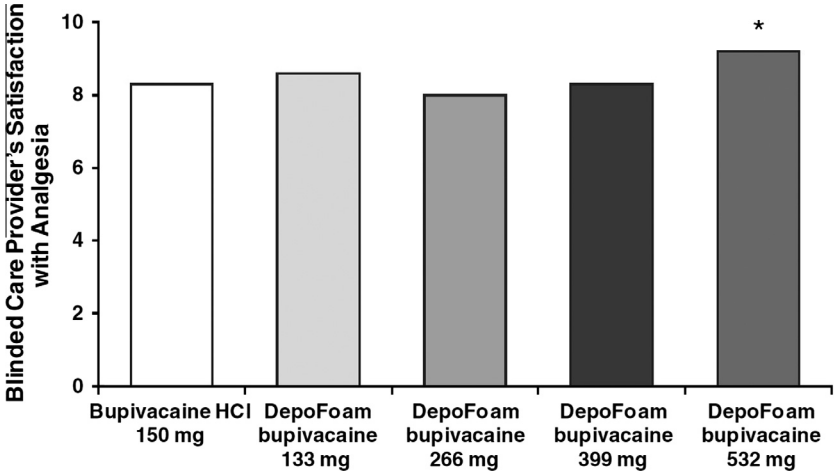

Figure 9 Mean blinded care provider's satisfaction with analgesia (rating scale: 0 = completely unsatisfied patients analgesia and 10 = completely satisfied patients analgesia) [62].

Soberón et al. [61] present the case of a 45 year old woman with digital ischemia (fingers 4 and 5) at the right hand. Axillary block was obtained by injecting 3 mL Exparel 1.3% [61]. They found that the results are superior to the subclavicular block due to a better pain control [61]. After surgery, photoplethysmography showed a normal ulnar artery and disappearance of finger cyanosis, which was due to the vasodilation effect created by liposomal bupivacaine [61–64].

Bramlett et al. [62] in a study on analgesic effect of liposomal bupivacaine in patients after total knee arthroplasty, describe replacing classical continuous femoral blocks [63] with liposomal bupivacaine Exparel, leading to increased patient comfort. They also note that for a proper analgesia up to 96 h 532 mg of Bupivacaine DepoFoam 1.3% in just one administration (Exparel™) is necessary [62] (Figs. 8 and 9).

5. Conclusions

The use of liposomal bupivacaine in order to obtain motor and sensory block represents a breakthrough in medical practice. Long-term analgesia in postoperative patients achieved by liposomal bupivacaine controlled release systems represents a great advantage for the safety and patient comfort. Therapeutical action of liposomal bupivacaine sustained up to 96 h after one administration without toxic concentration, well tolerated, without side effects and exhibited a predictable kinetic profile.

6. Conflict of interest

The authors have no conflict of interest to declare.

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