Adv Ther (2020) 37:2003–2016
https://doi.org/10.1007/s12325-020-01335-9

REVIEW

Postherpetic Neuralgia: Current Evidence on the Topical Film-Forming Spray with Bupivacaine Hydrochloride and a Review of Available Treatment Strategies

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Received: February 12, 2020 / Published online: April 15, 2020

ABSTRACT

Purpose of Review: This is a comprehensive review of the literature about the use of bupivacaine hydrochloride for the treatment of post-herpetic neuralgia (PHN). It briefly reviews the background, biology, diagnosis and conventional treatment for PHN, and then introduces and compares the recent evidence for the use of topical bupivacaine.

Recent Findings: PHN is defined by pain lasting 90 days or more after the initial presentation of herpes zoster ("Shingles", HZ) rash and is the most common complication of this disease. A product of re-activation of the Varicella-Zoster virus (VZV), HZ is diagnosed more than 1 million times annually in the United States. Approximately 20% of patients with HZ will experience PHN and will continue to suffer intermittent neuropathic symptoms, including

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itching and pain, that is sharp, stabbing, throbbing or burning, with the pain localized to the site of their original rash. This long-lasting pain compares with the severity of long-standing rheumatics and osteo-arthritis and is accompanied by severe allodynia causing significant suffering, and a financial burden that is manifested in both healthcare costs and loss of quality-adjusted life years. Prevention of PHN may be achieved with the Zoster vaccine, although there is still a large segment of unvaccinated population. Moreover, the Zoster vaccine is not always effective for prevention. Current treatment includes medical (systemic tricyclic antidepressants, anticonvulsants and opioids, topical lidocaine and capsaicin) and interventional (subcutaneous Botox injections, nerve blocks and nerve stimulation) therapies. These therapies are not always effective, and each carries their own profile of side effects and risks. Moreover, up to 50% of patients with PHN are refractory to management. Recent evidence is emerging to support the use of topical local anesthetics for the treatment of PHN. Two small studies recently found topical lidocaine spray to be effective in treating paroxysmal pain attacks associated with PHN. Bupivacaine is a longer-lasting local anesthetic, and a film-forming formulation allows easy and durable application to the affected skin. Recent studies show that topical film-forming bupivacaine is safe and as effective as lidocaine for the treatment of PHN. ***Summary***: PHN is an important though common complication of HZ and can cause long-lasting pain and disability. Current treatment for PNH is limited by efficacy and safety profiles of individual therapies. Recent evidence points to topical local anesthetics as an effective and safe alternative to conventional therapy. Film-forming bupivacaine may offer a durable and safe option for this otherwise difficult to treat syndrome.

Keywords: Bupivacaine; Film-forming systems; Herpes zoster; Lidocaine; Local anesthetics; Post-herpetic neuralgia; Shingles; VZV

Key Summary Points

Post-herpetic neuralgia (PHN) is an important though common complication of herpes zoster (HZ) and can cause long-lasting pain and disability.

Current treatment for PNH is limited by efficacy and safety profiles of individual therapies.

Recent evidence points to topical local anesthetics as an effective and safe alternative to conventional therapy.

Film-forming bupivacaine may offer a durable and safe option for this otherwise difficult to treat syndrome.

INTRODUCTION

The most common complication of herpes zoster (HZ; shingles) is postherpetic neuralgia (PHN). HZ is an infection caused by reactivation of dormant varicella zoster virus (VZV) in the sensory ganglia after a primary infection (chickenpox), usually during childhood [1]. It is characterized by a localized blistering rash and pain along the associated dermatome. PHN is defined as lingering pain for at least 90 days after the initial onset of HZ rash, and it significantly reduces the quality-of-life of affected patients [1, 2].

This is a comprehensive review of literature about the use of bupivacaine hydrochloride for the treatment of PHN. It briefly reviews the background, biology, diagnosis and conventional treatment for PHN, and then introduces and compares the recent evidence for the use of topical bupivacaine. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

EPIDEMIOLOGY

There are approximately 1 million cases of HZ annually in the US. It is more common among females than males (3.8 per 1000 person years to 2.6 per 1000 person.years) and the incidence increases with age, ranging from 1.1 per 1000 person.years in the 0–14 age group to 10.9 per 1000 person.years in the ≥ 80 age group [3]. Despite an effective vaccine introduced in 2006, a more recent study suggests no significant reduction in incidence, particularly in the older age group where the vaccine is recommended [4]. PHN occurs in approximately 20% of HZ patients, and more than 50% of PHN occurs in patients who are ≥ 60 years of age [1, 5]. Similarly, a population-based study in Olmsted county, MN, found that 18% of HZ patients developed PHN and that 83% of those patients were ≥ 50 years of age [6]. The frequency and the severity of PHN also increases with age, and is associated with the gradual decrease of cell-mediated immunity of VZV [7].

PATHOGENESIS

Although the pathophysiology of PHN is not clearly understood, animal and clinical studies have helped in determining its mechanisms. PHN is subcategorized into irritable nociceptor and deafferentation models [8]. During the reactivation of VZV, the virus replicates and spreads from the dorsal root ganglion to its respective periphery [9, 10]. The propagation elicits an immune response and inflammation that damages the peripheral nerve. This damage decreases the neuron's inhibition of pain, lowering the threshold for depolarization of pain signals [8, 10]. This results in painful perception in response to non-painful stimuli, a process called peripheral sensitization [8]. Studies have also shown an increased number and alteration of voltage-gated ion channels at the damaged peripheral nerves in rats with HZ [11]. This adds to the peripheral hyperexcitability of nociceptors shown in patients with PHN [10]. The chronic state of the mechanism is described as the irritable nociceptor model. It presents with pain with intact sensory function [8].

Repeated activation of subtype C-nociceptors also causes a heightened state of excitation in the dorsal horn. Direct viral damage by HZ weakens the descending inhibitory pain pathway, leading to a chronic activation of second-order neurons in the dorsal horn [8, 10]. Furthermore, loss of inhibitory gamma aminobutyric acid (GABA) interneurons in the dorsal horn has been reported in HZ patients with PHN when compared to HZ patients without PHN [10, 12]. These factors amplify all subsequent responses from the afferent input in a process called central sensitization. In PHN, this process is accompanied by the anatomical reorganization of low-threshold mechanoreceptive afferents, called Aβ-fibers [10, 13], that normally relay harmless tactile stimuli to the central nervous system [10]. When viral damage leads to the loss of C-nociceptors in the periphery, these fibers connect with second-order neurons that were originally wired to the C-nociceptor afferents in a compensatory manner. This process is called deafferentation, and patients present with allodynia with severe loss of sensory function [8, 10].

RISK FACTORS

A major risk factor for PHN is advanced age [14]. A 2016 meta-analysis showed relative risk estimates ranging from 1.22 to 3.11 for 10-year age increments. The study was inconclusive of gender differences as a major risk factor due to significant inter-study heterogeneity [14]. The analysis also found severe immunosuppression and diabetes mellitus as minor comorbid risk factors. Major risk factors of PHN associated with clinical manifestations of HZ involve pain before the onset of vesicular rash (prodromal pain), greater severity of rash and concurrent pain, and ophthalmic location of the HZ infection [14]. Interestingly, the duration of the prodromal pain or the rash is not significantly associated with PHN [15].

CLINICAL PRESENTATION AND DIAGNOSIS

Unlike the distinguishable clinical presentations of HZ, PHN is difficult to diagnose. Patients with PHN typically present with longer than 90 days of localized pain at the associated dermatome after the HZ rash has resolved [16]. The pain is intermittent and has sharp, itching, burning, throbbing, and stabbing qualities [17]. The severity of the pain is measured through standardized self-reported assessments and compares to chronic osteoarthritis and rheumatoid arthritis [18]. As mentioned previously, patients can have allodynia with or without the loss of tactile sensory function based on the mechanism [8]. Light touch or a brush of a cloth at the site of pain exacerbates the symptoms, and patients are often relieved with barriers to touch [16]. Therefore, patient history of a previous HZ and physical examination play a vital role in the diagnosis. Although PHN diagnosis does not depend on a laboratory test, viral culture or HZ antibody tests may be convincing [16].

FUNCTIONAL LIMITATIONS AND PSYCHOSOCIAL IMPACT

Unsurprisingly, PHN has a profound negative impact on the quality of life (QoL) of affected patients. Many patients attribute physical limitations such as walking, working, and sleeping in the Zoster Brief Pain Inventory, which is recognized as a reliable assessment tool for QoL of PHN patients [19]. Similarly, a French general population study found comparable QoL for HZ-related complications including PHN to that of chronic diseases, such as diabetes, chronic lung disease, and congestive heart failure [20]. PHN affects elderly patients, many of whom require subsequent hospitalization. These circumstances have negative social effects, reducing the autonomy of those in them [21]. Psychologically, patients report anxiety and depression primarily from the fear of recurrent pain [22]. Some patients even show suicidal ideations [20].

Functional complications of PHN also affect QoL. Common involvement of the ophthalmic region may cause ptosis, cataracts, and even blindness. Chronic peripheral nerve damage leads to neurological symptoms, such as facial paresis, hearing loss, and motor neuropathies [22]. Interestingly, a population-based cohort study found increased risk of coronary heart disease for patients with PHN [23]. These non-pain-related complications compound negatively on physical and psychosocial aspects of patients with PHN.

TREATMENT AND MANAGEMENT OF PHN

Several treatment options exist for the management of PHN, which include medications and interventional therapies [24, 25]. Systemic agents include tricyclic antidepressants (TCAs), calcium channel $\alpha_2\delta$ ligands (anticonvulsants), and opioids; topical agents include lidocaine and capsaicin [24]. Interventional therapies include subcutaneous injection of botulinum toxin type A (BTX-A), sympathetic nerve blockade, and transcutaneous electrical nerve stimulation (TENS) [26]. It is not uncommon for a combination of therapies to be used when managing PHN [27]. This section will provide an overview of common treatment options to highlight current approaches and limitations in the prevention and management of PHN.

Prevention

Although the content of this review is focused on treatment, it is important to note that prevention of PHN may be achieved through administration of the herpes zoster vaccine. There are currently two vaccines approved and recommended for use: a live-attenuated vaccine, zoster vaccine live (ZVL/Zostavax) and recombinant zoster vaccine (RZV/Shingrix), both of which the US Food and Drug Administration (FDA) has approved for use in adults 50 years and older [28]. In this demographic, the Advisory Committee on Immunization Practices recommends the two-dose RZV over

the single-dose ZVL due to increased efficacy and a longer duration of action in the prevention of herpes zoster and PHN [28]. These vaccines are not indicated for treatment in acute herpes zoster infection or PHN, and should be avoided until acute infection resolves [28].

Current Treatment Options

Tricyclic Antidepressants

TCAs are considered a first-line treatment of PHN and include the tertiary amine, amitriptyline, and secondary amines, nortriptyline and desipramine [24]. These drugs specifically inhibit the reuptake of norepinephrine and serotonin, and are believed to provide analgesia through inhibition of sensory perception in the central nervous system; they are also said to act on sodium channels and β-adrenergic receptors [29–31]. In a systematic review conducted by Finnerup et al. [18], placebo-controlled trials involving TCAs were evaluated in which 16 were deemed positive, resulting in a strong Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) with moderate quality of evidence [24]. This class of medications, however, is known to cause significant anticholinergic effects, sedation, and/or cardiac toxicity (more common with the tertiary amines) [27]. Given that drugs within the TCA class provide similar levels of pain relief, secondary amines may be preferred over tertiary amines due to fewer side effects [32].

Calcium Channel Ligands/Anticonvulsants

Calcium channel $\alpha_2\delta$ ligands are another class recommended as first-line treatment in the management of PHN [24]. Following evaluation of 39 placebo-controlled trials, they received a strong GRADE with high quality of evidence from Finnerup et al. [24]. This anticonvulsant class includes gabapentin (extended release formulations available) and pregabalin, which bind and cause inhibition at the $\alpha_2\delta$ subunit of voltage-gated calcium channels, causing an increase in GABA and a reduction in glutamate [27]. These medications have distinct uses in PHN as well as in other neuropathic pain syndromes, primarily taken chronically and in a dose-adjusted manner. In a systematic review performed by Wiffen et al., a majority of participants had either moderate or substantial benefit from gabapentin 1200 mg taken daily [33]. Side effects of this class include dizziness and somnolence, and, in patients with renal impairment, renal function should be monitored and dosing adjustments made accordingly [27]. Although anticonvulsants and TCAs are worthy first-line treatment options, the combination of gabapentin or pregabalin with a TCA may be a better alternative to monotherapy, as was demonstrated by Gilron et al. [34].

Opioids

Opioids are potent analgesics and exert their effects by acting as agonists at opioid μ-receptors located in the central nervous system. Tramadol is a weak μ-agonist and also inhibits norepinephrine and serotonin reuptake; it has a lower risk of misuse and abuse compared to the stronger opioids, but is said to be less efficacious and to lower the seizure threshold [35, 36]. Tramadol has questionable efficacy in the treatment of PHN, as evidenced by the results of an updated systematic review by Duehmke et al., which found low to very low quality evidence of benefit in "inadequate" studies [37]. In previous literature, strong opioids, such as oxycodone, morphine, and methadone, have shown better efficacy in pain relief compared to placebo and TCAs [38, 39]. A more recent systematic review by McNicol et al. questions the efficacy of opioids in neuropathic pain, stating "considerable uncertainty", and calls for more studies to be conducted [40]. Given the increased risk of misuse or abuse, adverse effects such as sedation and constipation, and limited evidence of efficacy in PHN, opioids are considered third-line drugs [27, 41, 42].

Capsaicin

Capsaicin is a neuropeptide derived from chili peppers, with an uncertain mechanism of action, administered as either a topical cream or a transdermal patch [43–45]. It is said to have an analgesic effect through disruption of cutaneous nociceptors [46]. Capsaicin cream is available in low concentrations, but its use is

associated with adverse reactions at the application site, such as burning and erythema, causing some patients to discontinue treatment [45]. It also requires multiple applications before a meaningful effect is appreciated. Furthermore, maximal analgesic effect may take several weeks to occur, which may limit adherence [45]. A high-concentration 8% capsaicin patch is available, with a concentration nearly 100 times greater than the low-concentration cream, which rapidly delivers the medication in a single application [47]. The patch has to be given by a healthcare provider (often in combination with a local anesthetic) and is administered at 3-month intervals [16]. An updated systematic review published in 2017 compared the 8% capsaicin patch to a control (0.4%) patch and found better pain improvement at both 8 and 12 weeks after administration, in addition to decreased pain intensity. However, the levels of evidence in these studies were rated moderate and very low [47].

Botulinum Toxin Type A

BTX-A inhibits acetylcholine release by disrupting fusion between acetylcholine-containing vesicles and the presynaptic membrane, and is given as a subcutaneous injection. It is believed that it exerts its analgesic effects by preventing release of substance P and calcitonin gene-related peptide, both of which are pro-inflammatory [48]. Apalla et al. conducted a small, placebo-controlled study to assess the efficacy, safety, and tolerability of BTX-A in the treatment of PHN, and found it successful in reducing pain, as measured by a visual analogue scale (VAS) score, with a maintained VAS score for a median time of 16 weeks [49]. The results of this study also showed improved quality of sleep as measured by a sleep score and good tolerability [49].

Sympathetic Nerve Blockade

The sympathetic nervous system has a significant role in pain mediation, although its role in PHN remains unclear [26, 50]. Prior studies evaluating efficacy of sympathetic nerve blockade showed some improvement of pain during acute zoster infection; however, they failed to show prolonged pain relief in PHN, yielding results described as "disappointing" with low quality of evidence [50]. These findings led to a recommendation against the use of this treatment in PHN [25].

Transcutaneous Electrical Nerve Stimulation

TENS involves a low-voltage electrical current applied to the skin with the intent of delivering pain relief to the area [51]. Its analgesic effect is said to be due to multiple mechanisms, including inhibition at the dorsal horn, descending pathway inhibition, and stimulation leading to endorphin release [26]. It is considered an adjunctive therapy; most studies evaluating TENS have it included as a combination therapy with a pharmacologic treatment, such as pregabalin, cobalamin, or lidocaine [52, 53]. One of these trials randomized patients to receive either pregabalin and TENS or pregabalin and a TENS placebo in which they were evaluated for pain intensity and sleep interference over a 4-week period [52]. The results showed a significant reduction in pain intensity and sleep interference in the pregabalin/TENS group [52]. Another trial assessed the efficacy of TENS, combined with local injections of cobalamin for pain reduction, and compared the results to participants who received TENS with local lidocaine injections, demonstrating that the cobalamin group had a significant analgesic effect compared to the lidocaine group [53].

LIMITATIONS OF CURRENT TREATMENTS

Current treatment options for the management of PHN pose several limitations. The pain associated with this condition is often treated unsuccessfully, side effects may lead to decreased tolerability and create safety concerns, and study designs are often inadequate, lacking sufficient evidence quality [16, 24, 26, 54].

One estimate states that upwards of 50% of patients with PHN have no response to treatment [54]. When evaluating trials that looked specifically at medication therapy, Dworkin

et al. found that half of patients do not experience "clinically meaningful pain relief" [27]. In certain cases, the ineffectiveness of therapy may be related to poor tolerability due to the side effects [16]. The average patient with PHN takes at least 5 medications for various comorbidities, and may experience potentiated side effects with the addition of PHN drugs [10]. The American Geriatrics Society recommends against the use of TCAs in the elderly, due to the associated side effects and drug interactions, which only further limits treatment options in this population [55]. Opioids are generally regarded as a third-line treatment, and long-term prescription of these drugs should be done with caution, given the sedative effects, high misuse and abuse potential, and current public health epidemic involving this class [24, 27, 56].

Study design and level of evidence are issues that impact the ability to make sufficient treatment recommendations [26]. In a systematic review performed by Lin et al., they were unable to identify a single best interventional treatment due to insufficient evidence, stating problems such as "unclear risk of bias" and potential publication bias [26]. A meta-analysis by Finnerup et al. also mentions the importance of accounting for potential publication bias, as it may overestimate treatment efficacy [24].

TOPICAL ANESTHETICS

Lidocaine

Lidocaine is a local anesthetic that provides pain relief through blockade of voltage-gated sodium channels, and can be administered topically as a gel, cream, plaster, or spray [57, 58]. An 8% lidocaine spray is available and was evaluated in 2 studies for quick-onset analgesia of paroxysmal pain associated with PHN, and found to be efficacious in both studies. However, these studies consisted of a small, short-term randomized cross-over trial and a case series [59].

Lidocaine medicated plaster (LMP) is available in a 5% concentration, and received FDA approval for the treatment of PHN in 1999, although its efficacy is debatable as evidenced by the conflicting conclusions in the literature [42, 60, 61]. The plaster contains 700 mg of lidocaine, and up to 3 non-overlapping plasters can be applied to the skin at once for a maximum of 12 h in a 24-h period [62]. The plaster allows the medication to be absorbed into the dermis and to act locally with minimal systemic absorption, thus decreasing the chances of drug interactions and often limiting side effects to minor skin irritation at the application site. For this reason, 5% LMP is considered first-line therapy in frail and elderly populations [24, 35, 62].

Lidocaine is quickly metabolized by the liver into less-potent active metabolites, monoethylglycinexylidide and glycinexylidide, which are then metabolized to 2,6-xylidine and eliminated by the kidneys [62–64]. Due to the hepatic processing of lidocaine and its antiarrhythmic properties, Bursi et al. conducted a study to assess safety in the chronic use of 5% LMP [62]. This was carried out by analyzing data from two phase III clinical trials of patients with PHN to determine the pharmacokinetics of lidocaine and its metabolites [62]. Their model did not predict any accumulation of lidocaine nor of its metabolites, and, therefore, they concluded that there should be no associated safety concerns [62]. These findings may be of significance for patients with hepatic dysfunction or taking Class I antiarrhythmic drugs, as previous literature recommended the avoidance of 5% LMP in these groups [12]. Furthermore, in a systematic review performed by Finnerup et al., the safety and tolerability of 5% LMP was regarded as "excellent in all cases" [24]. A Cochrane review published in 2014 included 12 studies consisting of participants with PHN and various neuropathic pain conditions to assess the efficacy and side effects of topical lidocaine compared to placebo or active control [58]. The reviewers stated that, although the studies were randomized and controlled, the quality of evidence was poor, lacking first-tier or second-tier evidence which prevented proper data analysis [58]. They were able to conclude that lidocaine plaster may be effective in treating pain associated with PHN and is well tolerated, at least in the short-term [58]. Given the uncertainty that remains in the efficacy of

topical lidocaine in PHN, increasing the number of large, high-quality studies that specifically evaluate its role in PHN, as opposed to several types of neuropathic pain, may provide some conclusiveness.

BUPIVACAINE AS A FILM-FORMING TOPICAL SPRAY

Neuropathic pain is caused by damage affecting the somatosensory nervous system, which results in localized signs and symptoms. Within the definition of neuropathic pain, there is stronger rational for the use of topical agents as a treatment option. Compared to parenteral routes of administration, topical treatments are administered through the skin and achieve localized therapeutic concentration at the site of application [65]. Furthermore, topical therapeutic approaches produce less systemic concentrations which translate to fewer systemic side effects and drug–drug interactions [65].

Despite many therapies available for topical and transdermal drug delivery, the desired drug concentration remains a limitation. Therefore, a need for improved drug delivery methods to penetrate the skin barrier, while still providing an effective therapeutic dosage to alleviate pain, are necessary. Recent advances in film-forming systems (FFSs) have been designed to solve the problem of fixed dosage forms in films and hydrogels. Controlled drug release FFSs contain a mixture of the drug, a film-forming polymer, and a solvent system that evaporates and allows the transformation of a thin film upon application to the skin [66]. A FFS provides the advantages of transdermal application of patches and hydrogels while overcoming the disadvantages of poor adherence to skin, poor permeability, and inaccuracy of dosing [66, 67].

FFSs in the form of topical metered-dose sprays have shown therapeutic concentrations of drug in the skin layers while providing antinociceptive efficacy. A study conducted by Ranade, et al. explored ropivacaine as a topical metered-dose spray in alleviating pain, and showed that the antinociceptive results were comparable to conventional lidocaine gel [67].

Mechanism of Action

Application of a FFS to the skin forms a transparent film upon evaporation of the volatile solvent, which results in an increase in the concentration of the drug with the possibility of supersaturated levels on the surface of the skin [68]. Drug flux through the skin is subsequently enhanced due to the increase in the thermodynamic activity of the FFS [68]. Furthermore, the non-volatile solvent component of the solvent system partitions into the stratum corneum layer of the skin and aids in drug diffusivity and enhancing permeation. This delivery system creates a reservoir of drug in the stratum corneum from which the drug can be slowly absorbed into circulation [68]. Therefore, drug permeation through the skin is improved compared to other transdermal or topical routes of application.

It is known that local anesthetics modulate pain by blocking impulses in peripheral nerves through inhibition of voltage-gated sodium channels. There is evidence that shows that topical anesthetics can also play a role in suppressing phosphorylation of extracellular signal-regulated kinases (ERK) in the dorsal horn of the spinal column. ERK activation in the spinal column is nociceptive activity-dependent and plays a critical role in signal transduction of the pain pathway [69]. In a study conducted by Yanagidate and Strichartz in 2006, they showed that the actions of bupivacaine on the suppression of capsaicin stimulation, ionotropic AMPA and NMDA receptors, and calcium ionophores ultimately inhibited ERK activation [69]. Further studies have confirmed the inhibition of bupivacaine on NMDA receptor-mediated transmission in the dorsal horn of the spinal cord [70]. Therefore, the heightened synaptic response as a result of central sensitization may be prevented by bupivacaine, and provides value in preventing chronic pain conditions [69, 70].

Film-Forming Bupivacaine Spray for PHN

PHN is a type of neuropathic pain that develops secondary to nerve injury and persists after

healing of skin rash subsequent to herpes zoster infection [65].

Since there are currently no treatment options that can reverse neuropathic nerve injury, treatments are strictly palliative in alleviating symptomatic pain. The lidocaine 5% patch is the only FDA-approved topical agent to provide symptomatic relief for PHN [65]. Despite this, the lidocaine patch is burdensome to use for patients. The patient is required to apply the patch to the most painful area of skin with the possibility of developing erythema and abnormal sensation at the site of application.

FFSs have been shown to be a novel method in drug delivery that offers an alternative to conventional transdermal and topical routes of application. The combination of the anti-nociceptive properties of a local anesthetic, such as bupivacaine, with the benefits of metered-dose film-forming spreay can provide innovative ways to treat neuropathic pain. Film-forming metered-dose sprays with bupivacaine as the active ingredient were explored in a patent published on October 19, 2017 by Grace Therapeutics [71]. Various formulations were investigated to discover an easy-to-use proprietary dermal spray formulation to overcome many of the disadvantages of current palliative treatments for PHN. This mode of therapy may prove to show clinical benefit, either in conjunction with well-studied conventional treatments or to patients with refractory PNH.

The topical spray formulation has the following components: a hydrophilic film-forming polymer, a hydrophobic film-forming polymer, a drug crystal precipitation inhibiting agent, an active agent, a pharmaceutically acceptable permeation enhancer, and a volatile solvent. The formulation is also capable of being sprayed as a unit dose onto skin via the use of a pump spray to provide a breathable, bio-adhesive, and microporous film. Additionally, the topical spray formulation provides a biphasic release of the active agent, in which the first portion is released, either immediately or after a short time delay, to provide a first peak maximum concentration at the site or in blood plasma, and a second portion of the active agent released after a lag time to provide a second peak maximum concentration [71].

In a series of experiments, the patent investigated various combinations of embodiments to curate a spray formulation with the most ideal drug permeation, droplet size distribution, and dose-proportional drug release. Drug permeation was tested in in vitro Franz Cell Strat-M synthetic membrane experiments. Based on one experiment, a combination of formulation assessing a hydrophobic polymer, such as Eudragit EPO, permeated the active agent less than the aqueous control. In a subsequent experiment, the use of a hydrophilic polymer, such as polyvinyl pyrrolidone or povidone (PVP), and ethanol as a solvent provided better permeation characteristics than the aqueous control. It was concluded that using a hydrophilic polymer is better than a hydrophobic polymer with respect to permeation and adhesion to the skin. In terms of permeation enhancers, it was concluded that oleyl alcohol significantly improved the initial rate of permeation [71].

Different formulations of the active agent, bupivacaine, were also explored on human cadaver skin. Based on the data, it was concluded that bupivacaine hydrochloride demonstrated superior permeation than bupivacaine base. Bupivacaine hydrochloride was further evaluated in an in vivo study in healthy rats to assess serum blood levels and characteristics of drug release based on the dose. Based on the results, the topical/transdermal drug delivery formulations of the invention have a biphasic release profile and is dose-proportional—a feature that is unique to the invention of polymeric bio-adhesive film spray [71].

Safety and Efficacy

A single dose crossover study to evaluate the pharmacokinetics and relative bioavailability of three doses of bupivacaine hydrochloride spray and bupivacaine injectable in 12 healthy male and female volunteers were conducted. Two treatments were administered to each subject. Each participant received either a single subcutaneous dose of bupivacaine hydrochloride 30 mg or a single topical dose of bupivacaine hydrochloride of 30 mg, 50 mg, or 70 mg. After

a 3-day washout period, subjects that were initially administered bupivacaine injectable then received either one of the three topical doses, while the latter half of participants then received the subcutaneous dose. Subjects were questioned if they felt the sensation of a Q-tip every 30 min after drug application for the first 8 h, or until sensation returned. It was concluded that both the injectable and topical spray showed similar results for the loss in sensation after Q-tip analysis, which suggests that the novel bupivacaine topical spray is equally efficacious as the reference subcutaneous injectable product [71].

An open-label study to evaluate the single-dose pharmacokinetics of bupivacaine topical spray in healthy male and female volunteers was conducted. The pharmacokinetic study was performed in 10 healthy human volunteers to assess the safety and tolerability of a 100-mg dose of topical bupivacaine. Skin irritation was assessed at the application site approximately 5 min, 6 h, and 24 h after dosing for each treatment. All 10 subjects showed no changes in their skin irritation assessments, and there was no evidence of irritation observed. Moreover, the drug delivery technology invention had a bi-phasic release profile similar to that observed in the rat study. This observed in-vivo bi-phasic drug release through the topical/transdermal route is unique to the invention [71]. It can be concluded based on these studies that the novel bupivacaine topical spray formulation is effective, safe, and well tolerated.

CONCLUSION

PHN is a painful complication of HZ. It is defined as chronic dermatomal pain for more than 90 days after the onset of the HZ rash. There are about 1 million cases of HZ in the US every year and 20% of those cases will present with PHN. Despite an effective vaccine, the incidence for PHN persists particularly in the elderly where the risk factors for PHN are higher. PHN negatively impacts the QoL on physical, functional, social, and psychological aspects. Current first-line treatments are topical anesthetics such as capsaicin or lidocaine, whereas more severe presentations are treated with anticonvulsants, antidepressants, opioids, botulism toxin A, sympathetic nerve blocks, and TENS. However, not enough evidence supports the safety and efficacy of some of the treatments. Increased economic burden and abuse potential also add to the current limitations. However, the use of biopolymeric film-forming bupivacaine spray may provide as an alternative treatment option, as it combines the efficient drug delivery potential of film-forming systems with the pharmacological actions of bupivacaine. Conducting more studies to further investigate the efficacy of this delivery method of bupivacaine is highly recommended.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Anh L. Ngo, Ivan Urits, Melis Yilmaz, Luc Fortier, Anthony Anya, Jae Hak Oh, Amnon A. Berger, Hisham Kassem, Manuel G. Sanchez, Richard D. Urman, Edwin W. Herron, Elyse M. Cornett and Omar Viswanath have nothing to disclose. Alan D. Kaye is a member of the journal's editorial board.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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