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REVIEW ARTICLE

Capsaicin in Pain Management

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ABSTRACT

Capsaicin is a pungent highly domesticated fat soluble alkaloid having its origin from Bolvia and Brazil. It acts by binding TRPV1 and shows wide applications in relief from neuropathic and musculoskeletal pain, post herpetic neuralgia, arthritic pain and cluster headache. Capsaicin has analgesic and anti-inflammatory properties and has been used in topical creams and gels for treating pain due to various conditions. Adverse effects include local discomfort characterized by burning, stinging and redness of the skin but systemic events are rare. Capsaicin is under development therapy for various diseases, it may develop as a new treatment therapy for a number of diseases in near future. A review is mainly focusing on its origin, chemistry, use, toxicity, mechanism, application and case study.

KEYWORDS

Capsaicin, Capsaicinoids, Pain, Application, Case Study

INTRODUCTION

Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the active component of chili peppers, which plants are belonging to the genus Capsicum. It is an irritant for mammals, including humans, and produces a sensation of burning in any tissue with which it comes into contact. Capsaicin and several related compounds are called capsaicinoids and are produced as secondary metabolites by chili peppers, probably as deterrents against certain mammals and fungi.[1]

Pure capsaicin is a hydrophobic, colorless, odorless, and crystalline to waxy compound. Capsaicin is synthesized in the interlocular septa of chilli peppers by addition of a branched-chain fatty acid to vanillylamine. Biosynthesis depends upon the AT3 gene, which is located at the pun 1 locus and which encodes a putative acetyl transferase.[2]

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IUPAC name for capsaicin is: 8-methyl-N-vanillyl 1-trans-6-nonenamide.Capsaicin is a phenylpropanoid compound.[3]

History

Origin of Capsaicin

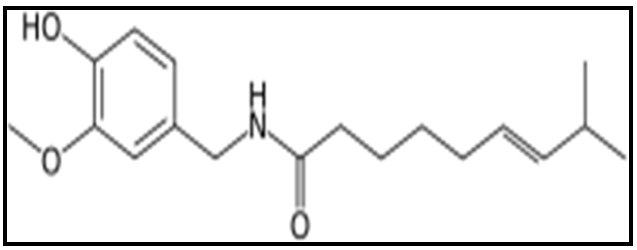
For thousands of years spices play a major role in various food preparations to strengthen the taste. Among various spices, the fruit of Capsicum, (Hot chili peppers) is the mostly used spice.[4] Capsaicin originated in Bolivia and parts of Brazil and has been domesticated for at least 7,000 years.[5,6] There is archaeological evidence at sites located in southwestern Ecuador that chili peppers were already well domesticated more than 6000years ago, and is one of the first cultivated crops in the America.[7] The centre of diversity for Capsicum is in South-Central South America with the majority of species having some range in Brazil and/or Bolivia. Some of the non-domesticated species are gathered for occasional use.[8-12] Capsaicin, a major alkaloid

among capsaicinoids produced only in Capsicum fruits.[13,10]

The genus Capsicum (family solanaceae) comprises of over 200 varieties ranging from the very hot habanero to the sweet bell peppers. These varieties are classified as “hot” or “sweet” based on Scoville “Heat” Units (SHU). The hotter the pepper is, the higher the SHU value.[14] The compound was first extracted (albeit in impure form) in 1816 by Christian Friedrich Bucholz (1770–1818). He called it "capsicin", after the genus Capsicum from which it was extracted. John Clough Thresh (1850–1932), who had isolated capsaicin in almost pure form,[15] gave it the name "capsaicin" in 1876.[16] But it was Karl Micko who first isolated capsaicin in pure form in 1898.[17] Capsaicin's empirical formula (chemical composition) was first determined by E. K. Nelson in 1919; he also partially elucidated capsaicin's chemical structure.[18] Capsaicin was first synthesized in 1930 by E. Spath and S. F. Darling.[19] In 1961, similar substances were isolated from chili peppers by the Japanese chemists S. Kosuge and Y. Inagaki, who named them capsaicinoids.[20,21]

Distribution of Capsaicin in the Fruit of the Plant

The highest concentrations of capsaicin are found in the ovary and in the lower flesh (tip) and the lowest content of capsaicin can be found in the seeds.[22] The gland on the placenta of the fruit produces capsaicinoids.[23] The majority, about 89%, of the capsaicin is associated with the placental partition of the fruit and nearly 5-6% in the pericarp and the seed.[24] Composition of capsaicin may vary among different varieties of same species and with fruit of a single variety.[25]



IUPAC Name

8-Methyl-N-vanillyl-trans-6-nonenamide

Other Names

(E)-N-(4-Hydroxy-3-methoxybenzyl)-8-methylnon-6-enamide,

Trans-8-Methyl-N-vanillylnon-6-enamide,

(E)-Capsaicin, Capsicine, Capsicin, CPS, C

Properties

- Molecular formula: $C_{18}H_{27}NO_3$
- Molar mass : 305.41 g mol^{-1}
- Appearance: crystalline white powder
- Odor : highly volatile and pungent
- Melting point: 62-65 °C, 335-338 K, 144-149 °F
- Boiling point : 210-220 °C, 483-493 K, 410-428 °F (0.01 Torr)
- Solubility in water 0.0013 g/100 ml
- Solubility: soluble in alcohol, ether, benzene slightly soluble in CS2, HCl, petroleum
- λmax: 280 nm
- Vapor pressure: very low
- Octanol- water partition coefficient (log $Kow)_7$: 3.04
- Henrys’ constant: 1 x 10_{-13} atm·m^3/mol at 25 °C
- Soil sorption coefficient $(Koc)_7$: 1.10 x $10^{3.\ 14}$

Capsaicinoids

Capsaicin is the main capsaicinoid in chili peppers, followed by dihydrocapsaicin. These two compounds are also about twice as potent to the taste and nerves as the minor capsaicinoids nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin. Capsaicin is believed to be synthesized in the interlocular septum of chili peppers by addition of a branched-chain fatty acid to vanillylamine; specifically, capsaicin is made from vanillylamine and 8-methyl-6-nonenoyl CoA.[26,27] Biosynthesis depends on the geneAT3, which resides at the pun1 locus, and which encodes a putative acyltransferase.[28]

Chemistry of Capsaicin

Capsaicin molecular structure has been first resolved by Nelson and Dawson in 1919.[29] Since the double bond seems to prevent the internal rotation thus capsaicin shows cis/trans isomerism. But mostly it is found in trans isomeric form because in cis form, the-$CH(CH_3)_2$ and the longer chain on other side of the double bond will be close together causing steric hindrance due to slight repulsion between them.[30]

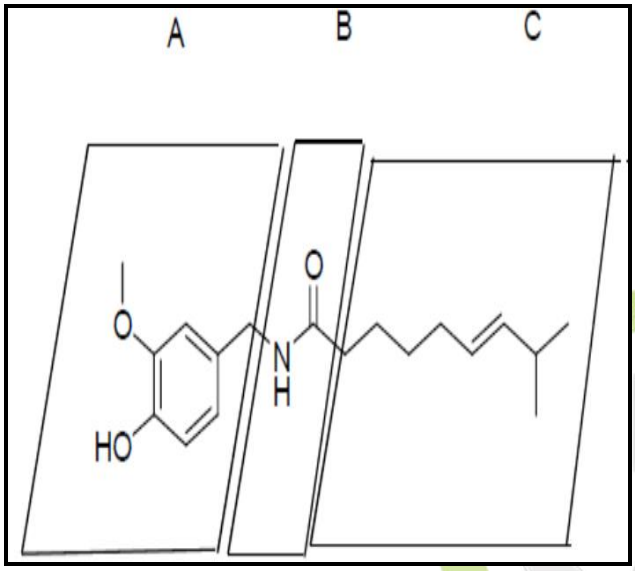


Figure 1: Regions of the molecule of capsaicin: A-aromatic ring, B-amidebond, and C-hydrophobic side chain

Structure Activity Relationship (SAR)

SAR studies can be rationalized by dividing capsaicin molecule into three regions: A (aromatic part), B (amide part), C (hydrophobic side chain). For potent agonist activity, substituent at 3 and 4 positions in the aromatic ring is necessary, and phenol 4-OH group in capsaicin analogue is of particular importance, H-bond donor/acceptor properties of the phenol group are important for the agonist activity.[31] C-region in structure (hydrophobic side chain) e.g. an octyl chain and substituted benzyl or group, is required for high potency. Optimally, such aralkyl groups are substituted in the para position of hydrophobic moieties.[32] It was reported that lateral chain lengths are important for the bioactivity of capsaicinoids, which was higher between 8 and 9 carbon atoms.[33]

USES

Food

Because of the burning sensation caused by capsaicin when it comes in contact with mucous membranes, it is commonly used in food products to give them added spice or "heat" (piquancy). The degree of heat found within a food is often measured on the Scoville scale.[34] There are many cuisines and food products featuring capsaicin such as hot sauce, salsa, and beverages.[35]

Less-lethal Force

Capsaicin is also the active ingredient in riot control and personal defense pepper spray chemical agents. When the spray comes in contact with skin, especially eyes or mucous membranes, it is very painful, and breathing small particles of it as it disperses can cause breathing difficulty, which serves to discourage assailants. In large quantities, capsaicin can cause death. Symptoms of overdose include difficulty breathing, blue skin, and convulsions.[36]

Pest Deterrent

Capsaicin is also used to deter mammalian pests. Specific targets of capsaicin repellants are voles, deer, rabbits, squirrels, insects and attacking dogs.[37]

Equestrian Sports

Capsaicin is a banned substance in equestrian sports because of its hyper sensitizing and pain relieving properties. At the show jumping events of the 2008 Summer Olympics, four horses tested positive for the substance, which resulted in disqualification.[38]

Medical

Capsaicin is currently used in topical ointments, nasal sprays (Sinol-M), as well as a high-dose dermal patch (trade name Qutenza), to relieve the pain of peripheral neuropathy such as post-herpetic neuralgia caused by shingles[39]. The capsaicin remains on the skin until the patient starts to feel the "heat", at which point it is promptly removed. Capsaicin is also available in

large bandages (plasters) that can be applied to the back.

In 2009, a landmark clinical trial performed at the Institute for Allergy & Asthma concluded that Sinol-M Nasal Spray was effective for the treatment of allergic rhinitis. This made Sinol-M the first all-natural, clinically proven nasal spray for allergies. "This study represents the first-ever capsaicin-based treatment for allergic rhinitis to be supported by prospective clinical data, and has important implications for millions of Americans who suffer from nasal allergies. This all-natural product has now been demonstrated to provide clinical effectiveness without any of the side effects associated with intra-nasal steroids and is available without a prescription" said Michael A. Kaliner, of the Institute of Asthma and Allergy in Wheaton, Maryland[40,41]. There is also a Sinol-M capsaicin based nasal spray for the relief of headache pain (migraine, sinus, cluster, tension and premenstrual). This is the first OTC nasal spray for headache relief. Capsaicin creams are used to treat psoriasis as an effective way to reduce itching and inflammation.[42,43]

According to animal and human studies, the oral intake of capsaicin may increase the production of heat by the body for a short time. Due to the effect on the carbohydrates breakdown after a meal, cayenne may also be used to regulate blood sugar levels[44]. The American Association for Cancer Research reports studies suggesting capsaicin is able to kill prostate cancer and lung cancer cells by causing them to undergo apoptosis[45]. The studies were performed on tumors formed by human prostate cancer cell cultures grown in mouse models, and showed tumors treated with capsaicin were about one-fifth the size of the untreated tumors. There have been several mouse studies conducted in Japan and China that showed natural capsaicin directly inhibits the growth of leukemic Cells[46]. Capsaicin is also the key ingredient in the experimental drug Adlea, which is in Phase 2 trials as a long-acting analgesic to treat post-surgical and osteoarthritic pain for weeks to months after a single injection to the site of pain Moreover, it reduces pain resulting from rheumatoid arthritis as well as joint or muscle pain from fibromyalgia or other causes.[47]

Toxicity

Acute Health Effects

Capsaicin is a highly irritant material requiring proper protective goggles, respirators, and proper hazardous material handling procedures. Capsaicin takes effect upon skin contact(irritant, sensitizer), eye contact (irritant), ingestion, and inhalation (lung irritant, lung sensitizer).The LD50 in mice is 47.2 mg/kg.[48] They cause burning or stinging pain to the skin, and if ingested in large amounts by adults or small amounts by children, can produce nausea, vomiting, abdominal pain and burning diarrhea. Eye exposure produces intense tearing, pain, conjunctivitis and blepharospasm.[49] When used for weight loss in capsules, there has been a report of heart attack; this was thought to be due to excess sympathetic output.[50]

Treatment after Exposure

For external exposure, bathing the mucous membrane surfaces that have contacted capsaicin with oily compounds such as vegetable oil, paraffin oil, petroleum jelly (Vaseline), creams, or polyethylene glycol is the most effective way to attenuate the associated discomfort; since oil and capsaicin are both hydrophobic hydrocarbons the capsaicin which has not already been absorbed into tissues will be picked up into solution and easily removed. Capsaicin can also be washed off the skin using soap, shampoo, or other detergents. Capsaicin is soluble in alcohol, which can be used to clean contaminated items.[36] Additionally when ingested, cold milk is an effective way to treat the burning sensation (due to caseins having a detergent effect on capsaicin); and room temperature sugar solution (10%) at 20°C (68 °F) is almost as effective.[51] Burning and pain symptoms can also be relieved by cooling, such as from ice, cold water, cold bottles, cold surfaces, or a flow of air from wind or a fan. In severe cases, eye burn might be treated symptomatically with topical ophthalmic anesthetics; mucous membrane burn with lidocaine gel. The gel from the aloe plant has

also been shown to be very effective. Capsaicin-induced asthma might be treated with nebulized bronchodilators or oral antihistamines or corticosteroids.[49]

Effects of Dietary Consumption

Ingestion of spicy food or ground jalapeño peppers does not cause mucosal erosions or other abnormalities.[52] Some mucosal micro bleeding has been found after eating red and black peppers, but there was no significant difference between aspirin (used as a control) and peppers.[53]

Effects on Weight Loss and Regain

There is no evidence showing that weight loss is directly correlated with ingesting capsaicin, but there is a positive correlation between ingesting capsaicin and a decrease in weight regain. The effects of capsaicin are said to cause "a shift in substrate oxidation from carbohydrate to fat oxidation". This leads to a decrease in appetite as well as a decrease in food intake.[54] Short-term studies suggest that capsaicin aids in the decrease of weight regain. However, long-term studies are limited because of the pungency of capsaicin.[55] Another recent study has suggested that the ingestion of capsaicinoids can increase energy expenditure and fat oxidation through the activation of brown adipose tissue (BAT) in humans from the effects of the capsaicin.[56]

Mechanism of Action of Capsaicin in Pain Management

Capsaicin acts by binding to transient receptor potential vanilloid 1 (TRPV1), previously known as the vanilloid receptor, which is mainly expressed in the sensory neurons.[57] This receptor is located primarily in the small fibers of nociceptive neurons. It is non-selective in nature and is ligand operated cationic channel. TRPV1 is also broadly distributed in tissues of the brain, bladder, kidneys, intestines, keratinocytes of epidermis, glial cells, liver, and polymorph on nuclear granulocytes, mast cells, and macrophages.[57-58] TRPV1contains 838 amino acids and has a molecular weight of 95 kDa in humans, consisting of six transmembrane domains with a short pore-forming region between the fifth and sixth transmembrane domains.[59] It regulates intracellular calcium levels by coupling with a nonspecific cation channel permeable to sodium and calcium ions, and is located in the plasma membrane and the endoplasmic reticulum.[60-61] Endogenous substance like endovanilloids can regulate and activate this channel and diverse exogenous stimuli which includes chemical agonists as capsaicin, olvanil and resiniferatoxin, ligands highly lipophilic that share structural similarity to several endogenous fatty acids identified asTRPV1 agonists.[62] Compounds that are used as antagonist for TRPV1, includes capsazepine, iodoresiniferatoxin, ruthenium red, A-425619, SB-366791, AMG9810 andSB-705498.[63] A heat sensitive subunit of TRPV1 is responsible for burning sensation caused by capsaicin.

When capsaicin binds to TRPV1, Activation of TRPV1 by capsaicin results in sensory neuronal depolarization, and can induce local sensitization to activation by heat, acidosis, and endogenous agonists. Topical exposure to capsaicin leads to the sensations of heat, burning, stinging, or itching. High concentrations of capsaicin or repeated applications can produce a persistent local effect on cutaneous nociceptors, which is best described as defunctionalization and constituted by reduced spontaneous activity and a loss of responsiveness a wide range of sensory stimuli, causes analgesic action.[64]

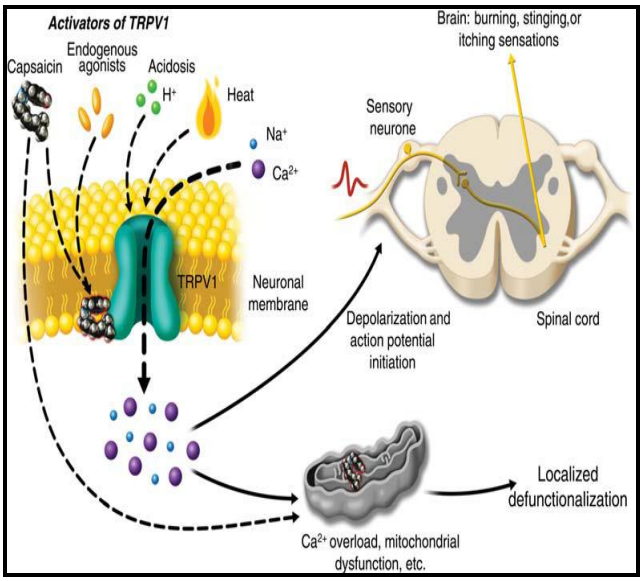


Figure 2: Mechanism of capsaicin in pain management

Applications of Capsaicin in Pain

Capsaicin May Help Relieve Pain From

- Pain disorders, including pain after surgery.
- Nervous system problems such as ,
- Diabetic neuropathy,
- Trigeminal neuralgia, and
- Postherpetic neuralgia (shingles).
- Cluster headaches.
- Joint problems such as osteoarthritis and rheumatoid arthritis.
- Skin conditions such as psoriasis.
- Mouth sores due to chemotherapy or radiation.
- Muscle pain such as post mastectomy pain.

Formulations of Capsaicin

Formulations of capsaicin available in various dosage form such as,

- Cream
- Dermal patch
- Gel
- Spray
- Lotion

Marketed Preparations

Dosage Form	Marketed Preparations	Uses
Cream	Capsaicin	Arthritis Pain Relief
	Capzasin-Hp	Arthritis Pain Relief
	Zostrix	Arthritis Pain Relief
	Golden Tiger	Muscular& Arthritis Pain
Dermal Patch	Qutenza	Neuropathic Pain
	Wellpatch	Multipurpose Relief Of Aches &Pains
	Salonpas	For Minor Aches And Pain Relief
Gel	Capzasin	Arthritis Pain Relief
	Fast Arthritis Aid	Arthritis Pain Relief& Muscle Pain
Spray	Sinol	Fast Headache Relief
	Painazin-Cp	Arthritis Pain Relief
	Sinus Plumber Nasal Spray	For Congestion, Headache, Allergies
Lotion	Castiva	Arthritis Pain Relief
	Capsika	Muscle Pain Relief

Drawback of Formulations

- severe burning or irritation where the medicine was applied
- skin redness where the medicine was applied; or
- trouble breathing or swallowing (after accidental inhalation of capsaicin odor or dried residue)
- Less serious side effects may include a mild burning sensation that can last for several hours or days, especially after your first use of capsaicin topical.

To Make the Application of the Cream More Bearable

- These side effects are minor, and many patients tolerate them because of the improvement they have in their pain relief.

- To make initial application of the stronger cream (Axsain) more bearable, your pain clinic doctor may give you some anaesthetic cream to apply to the area where you are later going to apply the capsaicin ointment.[65]

CASE STUDY

A Case Study in the Use of Capsaicin in the Treatment of Neuropathic ChestWall Pain and Post-Thoracotomy Intercostal Neuralgia

Introduction

A 57 year-old male with chronic post-thoracotomy pain was treated with 8% Qutenza® in an off label topical application. Qutenza® patch contains 8% capsaicin (640mcg/cm^2), with each patch (log Kow) 7: containing a total of 179 mg of capsaicin. It has FDA approval for use in the treatment of post herpeticneuralgia.[66] The goal was to evaluate the effectiveness of Qutenza® for the treatment of neuropathic chest wall pain. Though the initial benefit reported by the patient was excellent, the duration of the response was limited.

Patient History and Treatment Modalities

The patient is a 57 year-old male previously diagnosed with chronic left chest wall pain and post-thoracotomy (intercostal) neuralgia. The patient was thrown while training a horse April 17, 2010, resulting in fracture of the left transverse process from T6-L5,fracture of spinous process at T4 and T8-T12, fracture at the right inferior endplate of L4and L5, left clavicle fracture, comminuted left scapular fracture, left pneumothorax, splenic laceration, and multiple left rib fractures (flail chest) (Figure 3). The patient was managed surgically with a left thoracotomy for rib-plating 4-9, chest tube placement, and mechanical ventilation (Figure 4). Subsequent treatment is subject to acceptable modalities mandated in accordance with Workman's Compensation rules.

Treatment Rationale

Qutenza® (capsaicin) 8% patch is indicated for the treatment of neuropathic pain associated with postherpetic neuralgia. Transient receptor potential vanilloid type 1(TRPV1) is involved in the peripheral and central mechanisms of visceral sensitization in man. Because capsaicin is known to selectively bind with TRPV1, Qutenza® was selected for trial in an off label administration in post- thoractomyneuralgia.[67-71]

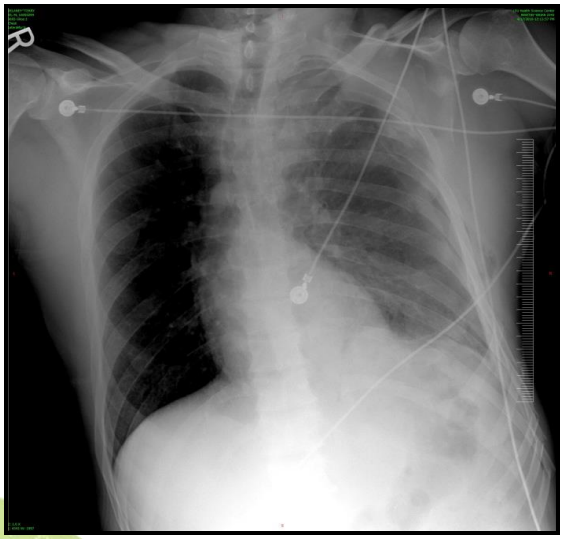


Figure 3: Pre-operative flail chest and pneumothorax

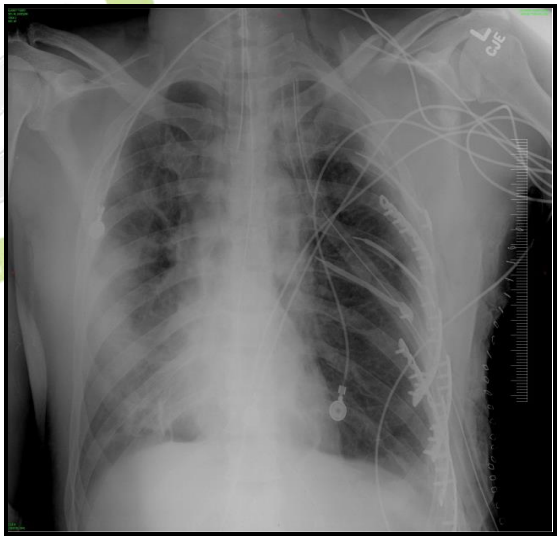


Figure 4: Post-operative repair

Procedure, Materials and Methods

Written informed consent was obtained from the patient. With the patient in a sitting position, the affected region on the left thorax, axilla and anterior chest wall were delineated with a marker. These areas were then cleansed and prepped with chlorohexidine scrub. Regional hair was removed with scissors and paper tape. Lidocaine4% (EMLA) cream was then applied

generously to an approximate 7-inch × 9-inch area on the left thorax, near the incision site. This pre-treatment was administered to reduce the discomfort associated with the application of Qutenza® patch (8% capsaicin). The EMLA cream remained on the affected area for 75 minutes then removed by cleansing with mild soap and water and the skin dried. After the skin preparation was complete, the Qutenza® patch containing 8% capsaicin was cut, tailored, and fit-ted to the affected area on the left thorax/chest wall. The patch was then covered and secured in place with circumferentially applied gauze dressing for 65 minutes. After completion of the 65-minute application time, the Qutenza® patch was removed. The area was cleansed with cleansing gel provided with the patch, then the remainder wiped off. The skin was then gently washed and dried.

Results

The patient reported immediate relief. Pre-procedure pain score was 8 on a 10-pointscale; the 30-minute post procedure pain score was 2-3 on the 10-point scale. When seen for evaluation one week post-procedure, the patient reported complete pain relief for the initial 48 hours. The symptoms then gradually returned to the pre-procedure level in the subsequent five days.

Discussion

Capsaicin has been proven to be very effective in treating post-herpetic neuralgia. Currently, compound NGX- 4010, 8% topical capsaicin (Qutenza®) is FDA approved for treatment of post-herpetic neuralgia. A single one- hour application can provide up to three months of relief for those suffering from PHN. This therapy is well tolerated, non-invasive and provides a much-needed therapeutic option for those suffering from this type of chronic pain. Briefly, the mechanism of action of this drug is thought to lie in its ability to selectively stimulate unmyelinated C-fibers and cause the release and subsequent reversible depletion of substance P and possibly other neurotransmitters.[72] While the mechanism of post-thoracotomy pain and resulting intercostal neuralgia is quite different from that of post herpetic neuralgia (physical trauma versus infective), the pain transmission pathways remain the same. It was our hope in this trial that capsaicin would also alleviate the pain associated with this type of neuralgia. While the 8%capsaicin treatment provided a profound reduction in pain for this patient, the results were short- lived, lasting only approximately 48 hours. A literature search for the use of8% capsaicin for the treatment of intercostal neuralgia did not reveal any results and therefore we wish to bring attention to its potential use for this type of pain. While further research is necessary regarding the use of capsaicin for this purpose, it holds promise as a potential treatment and at least warrants further study as a therapeutic option in intercostal neuralgia.

Efficacy of qutenza (capsaicin) 8% patch for neuropathic pain: a meta-analysis of the qutenza clinical trials database Pain, Clinical Article

Qutenza is a capsaicin patch used to treat peripheral neuropathic pain, including postherpetic neuralgia (PHN) and HIV–associated neuropathy (HIV–AN). The Qutenza Clinical Trials Database has been assembled to more fully characterize the effects of Qutenza. The authors conducted a within–subject meta–analysis of Qutenza studies to further define the medication's efficacy profile across studies. The results confirm that Qutenza is effective for the treatment of both PHN and HIV–AN comparedto low–dose control patch.

Methods

- The meta–analysis combined individual patient data from randomized, controlled studies of Qutenza in peripheral neuropathic pain (1458 subjects treated with approved doses of Qutenza or control patches; 1120 with PHN and 338 with HIV–AN).

Results

- These 7 studies had similar designs and were performed with the high–dose 8 % Capsaicin Qutenza patch and a 0.04 % low–dose control patch.

- The difference between treatment groups for the primary efficacy endpoint of % Change from baseline to Weeks 2–12 on pain intensity score was calculated.
- "Responders" were defined as subjects with 30% decrease in mean pain intensity score during Weeks 2–12.
- The overall between–group difference in% change from baseline in pain intensity was 8.0% (95% confidence interval: 4.6, 11.5; P<0.001), which statistically significantly favored Qutenza over low–dose control.
- Qutenza superiority was demonstrated for both PHN and HIV–AN patients for the primary endpoint and the endpoint proportion of 30% pain reduction responders, and for PHN patients for the endpoint of proportion of 50% pain reduction responders.[73]

The capsaicin 8% patch for neuropathic pain in clinical practice: a retrospective analysis Pain Medicine, Clinical Article

The study aims to investigate the response of patients with peripheral neuropathic pain (PNP) to capsaicin 8% patch treatment in a clinical setting. This analysis demonstrates that in clinical practice, the capsaicin 8% patch provides rapid and sustained pain reductions in patients with a variety of PNP conditions and a significant reduction in prescribed concomitant NP medications. The capsaicin 8% patch can be a valuable addition to the NP treatment armory for certain patients.

Methods

- Patients diagnosed with PNP who attended the clinic for capsaicin 8% patch treatment between January 13, 2010 and February 7, 2011.
- Pain intensity was assessed using the Numeric Pain Rating Scale (NPRS) at baseline and following each capsaicin 8% patch treatment.
- Changes in prescribed concomitant neuropathic pain (NP) medications and response duration were recorded.

Results

- Overall, 68 patients with PNP conditions, including facial neuropathy (severe trigeminal neuralgia in V2), polyneuropathy, post-herpetic neuralgia, and mono neuropathies, received 96 treatments with the capsaicin 8% patch.
- The 53 patients with a follow-up of ≥8weeks demonstrated a 48.4% mean reduction in NPRS score from baseline to Weeks 1–8.
- Among the 37 responders (those exhibiting ≥30% reduction in NPRS score from baseline to Weeks 1–8), the median time to re-treatment was 125 days.
- Following treatment, there was a significant (P<0.001) 54% reduction in the mean number of prescribed concomitant NP medications taken by patients.[74]

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