

NEUROPATHIC PAIN SECTION

Case Report

Successful Treatment of Refractory Postherpetic Neuralgia with Topical Gallium Maltolate: Case Report

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Abstract

Introduction. Postherpetic neuralgia is a common sequela of herpes zoster (shingles), in which chronic pain may last for weeks to years. Currently available treatments include systemic opioid analgesics, tricyclic antidepressants, corticosteroids, and anticonvulsants, as well as topical capsaicin and lidocaine. These treatments are commonly unsatisfactory, with fewer than half of treated patients experiencing more than a 50% reduction in pain.

Case. A 99-year-old woman had a 4-year history of severe postherpetic (trigeminal) neuralgia on the left side of her face. During those 4 years, numerous treatments were tried, including systemic opioid analgesics and anticonvulsants, and topical lidocaine and capsaicin, all with unsatisfactory results. The topical application of gallium maltolate, at a concentration of 0.5% in an emulsion of water and hydrophilic petrolatum, was found to relieve the severe pain within about 10 minutes, with the relief lasting for about 6–8 hours. The patient has been using this treatment for more than 5 years, with no adverse effects and a highly significant improvement in her quality of life.

Discussion. Gallium has significant anti-inflammatory activity, inhibiting the activation and proliferation of pro-inflammatory T cells. Because gallium is chemically similar to zinc, it can interfere with the activity of matrix metalloproteinases (zinc-bearing proteases), which have been implicated in the etiology of neuropathic pain, and it may suppress the secretion of substance P. Gallium may also inhibit viral replication and the inflammatory activity of viral proteins. This case provides ratio-

nale to study topical gallium maltolate in patients with refractory peripheral neuropathic pain.

Key Words. Postherpetic Neuralgia; Trigeminal Neuralgia; Neuropathic Pain; Gallium Maltolate; Gallium

Introduction

Postherpetic neuralgia (PHN) is a neuropathic pain that persists following the resolution of an occurrence of herpes zoster (shingles). The virus that causes herpes zoster, varicella-zoster virus, remains latent in dorsal root or trigeminal ganglia following an earlier varicella (chickenpox) infection, and may become reactivated with age or the weakening of immune responses. Following reactivation, viral particles travel down neuronal axons to the skin, producing painful, vesicular cutaneous lesions that are dermasomally distributed. Pain is usually also present before the skin lesions form (prodromal pain), when the multiplying virus is already damaging neurons. PHN occurs in about 40% of herpes zoster patients who are older than 50 years and about 75% of those over 75 [1]. The duration of PHN ranges from weeks to years; both the incidence and duration of PHN are strongly positively correlated with age [2].

The etiology and pathophysiology of PHN are not fully understood. Fields et al. [3] suggested two broad types of PHN: 1) severe allodynia caused by abnormal hypersensitivity and activation of C (unmyelinated) primary afferent nociceptor neurons, with no loss of sensation; and 2) variable degrees of allodynia associated with partial loss of C-nociceptors, resulting in partial loss of sensation, in which the pain is caused by spontaneous discharge of deafferented central neurons. Patients having the first type of pain (“irritable nociceptor”) would tend to respond to local anesthetic treatment, whereas those with the second type (“deafferentation”) would not. Other studies, based on autopsy results, have found that viral replication and/or proteins may persist in sensory neurons following herpes zoster resolution, potentially causing persistent pain [1]. All current information indicates that the pathophysiology of PHN is complex, multifactorial, and variable, accounting for the variable and commonly resistant nature of PHN to treatment.

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The development of herpes zoster, and of consequent PHN, is significantly reduced in immunocompetent individuals who receive herpes zoster vaccine [4]. Treatment of herpes zoster with oral nucleoside antiviral agents (e.g., acyclovir, valacyclovir, and famciclovir), if initiated within 72 hours of lesion onset, can reduce viral shedding, speed healing of cutaneous lesions, and reduce acute pain [5]. Such treatment may reduce the incidence, duration, and severity of PHN, though a meta-analysis of six randomized controlled trials found no significant difference in the incidence of PHN (at 4 or 6 months after herpes zoster rash onset) between patients who took acyclovir and those who took placebo [6].

Available systemic treatments for PHN include opioid analgesics, tricyclic antidepressants (particularly amitriptyline), corticosteroids, and the anticonvulsants gabapentin and pregabalin. Topical treatments include capsaicin, lidocaine, acetylsalicylic acid, and geranium oil. All of these therapeutics have limited efficacy, and most can produce significant adverse effects [5]. Current PHN therapy is generally considered unsatisfactory, with less than half of treated patients experiencing pain reduction of greater than 50% [7]. As PHN afflicts an estimated 800,000 people in the United States alone [2], new, more effective treatments are needed.

Case Report

This case report describes the course and treatment of PHN in a female patient who was 95 years old at the time of initial presentation, and is currently 105. The patient initially presented with severe pain on the left side of her face and moderate edema of her lips. Because she had dental work performed earlier the same day (an upper left molar crown was repaired), and other signs of disease were not noted, it was hypothesized that her pain and edema were likely related to the dental work, and she was referred back to her dentist.

Two days later, the patient's facial pain had worsened. She went to the emergency room, where she received x-rays of her head. The attending physician concluded that the patient had an infected root canal, and she was referred to an endodontist. The endodontist drilled out the presumably infected tooth, but no obvious infection was found; no drainage ensued from the tooth and pain relief did not occur.

On the evening of the third day after initial presentation, the patient returned to the emergency room with severe left-side facial pain. At that time, the patient received the correct diagnosis of herpes zoster (a vesicular rash had appeared), and was sedated with morphine. She began a 4-day course of acyclovir, a 3-day course of prednisone, and was told to apply lidocaine 5% patches and capsaicin 0.025% cream to the affected area for 3 days. The herpes zoster rash resolved in about a week, but severe PHN persisted, affecting the dermatome corresponding to the mandibular branch of the left trigeminal nerve.

The patient experienced essentially no remission in her left-side facial pain over the following 4 years. During that time, the patient tried numerous treatments in an attempt to relieve the pain. Systemic therapeutics that were used included amitriptyline 25 mg bid, methadone 5 mg bid, carbamazepine 100 mg bid, gabapentin 200 mg qd, oxycodone 20 mg bid, hydrocodone bitartrate 5 mg/acetaminophen 500 mg qid, naproxen, acetaminophen, and intravenous hydrogen peroxide; topical therapeutics included lidocaine 5% patches, capsaicin 0.025% cream, geranium oil, and emu oil. None of these treatments provided significant, satisfactory pain relief, and the patient was hospitalized several times due to severe pain. After 4 years, her left-side facial pain was still severe and there was noticeable left-side facial erythema. The patient, who had been highly active before the onset of PHN (playing tennis at the age of 95), was depressed and discouraged due to her chronic PHN and her consequent reduction in activity.

Four years and 2 months after initiation of the patient's PHN, the patient was given, by the patient's son, a topical cream consisting of 0.5% gallium maltolate in an emulsion of 50% water and 50% Aquaphor® (Beiersdorf Inc., Wilton, Connecticut, USA) (hydrophilic petrolatum). The gallium maltolate had been synthesized under cGMP protocols by Regis Technologies, Inc., of Morton Grove, Illinois. The patient utilized the cream by gently applying a thin coating to the painful area on the left side of her face.

The patient said that when the gallium maltolate cream was first applied, her facial pain was virtually eliminated within about 10 minutes. This effect lasted for about 6–8 hours. After several days of applying the cream three times per day, her facial erythema had gone away. Since that time, more than 5 years ago, the patient has applied the cream two to four times per day nearly every day for pain relief. Her severe pain is nearly eliminated by the cream, though mild allodynia sometimes still remains. When offered the chance to try new analgesic treatments, she has refused, saying that she is doing fine on her gallium maltolate cream. From the time that the patient started using the topical cream, she has returned to an active lifestyle with a greatly improved quality of life. No adverse effects were noted by the patient, and none were observed during physical examination or by routine tests. The patient has noted that the gallium maltolate cream has also rapidly relieved pain from insect bites, spider bites, abrasions, and minor burns.

A placebo effect in this patient is considered unlikely. No significant pain relief had occurred during 4 years in which numerous drugs were tried, most having been prescribed by her physician, but some also obtained from alternative medical sources. Furthermore, a week before receiving the gallium maltolate cream, the patient tried a topical formulation, given to her by her son, consisting of the same vehicle used for the gallium maltolate cream, but containing a trace of a germanium compound; this formulation produced no pain relief. The gallium maltolate cream has consistently provided temporary pain relief, which lasts for several hours following administration, over a period of more than 5 years.

Discussion

Gallium is known to have antiproliferative, anti-inflammatory, and anti-bone-resorptive activities [8,9], and topically applied gallium nitrate has been reported effective in relieving arthritis pain [10]. During small clinical anticancer trials, significant pain relief was noted in prostate cancer patients [11] and multiple myeloma patients [12] who received parenteral gallium nitrate. Severe right abdominal pain was relieved following oral administration of gallium maltolate in a patient with advanced hepatocellular carcinoma [13]. We here present the first published report of topically applied gallium having an analgesic effect other than on inflammatory arthritis, and the first published report of topically applied gallium showing efficacy against neuropathic pain.

The antiproliferative activity of gallium appears due mainly to its chemical mimicry of ferric iron (Fe^{3+}) [8]. Fe^{3+} is present in the active site of ribonucleotide reductase, an enzyme essential for DNA synthesis. Because gallium (which occurs in solution as Ga^{3+}) is an irreducible analog of ferric iron, it interferes with cellular uptake and usage of Fe^{3+} , consequently inhibiting ribonucleotide reductase activity and DNA synthesis. Like Fe^{3+} , gallium binds to serum transferrin and is then taken up by pathological rapidly proliferating cells that overexpress transferrin receptor, such as cancer cells and bacteria. The inhibition of DNA synthesis in these cells prevents replication and ultimately results in cell death.

Some of the observed anti-inflammatory activity of gallium is also likely related to gallium being an irreducible mimic of Fe^{3+} . Several animal and *in vitro* studies found gallium to be a potent inhibitor of T cell activation and proliferation [8]. T-helper type 1 (Th-1) cells, which generally act to stimulate macrophages and are predominately pro-inflammatory, are much more sensitive to inactivation by iron deprivation than Th-2 cells, which act mainly on B cells to stimulate antibody production and are predominately anti-inflammatory [14]. The presence of gallium, by competitively inhibiting iron, would tend to cause inactivation of Th-1 cells relative to Th-2 cells.

The varicella-zoster virus itself is dependent upon ribonucleotide reductase (and therefore Fe^{3+}) to synthesize DNA and multiply; unlike most viruses, it produces its own ribonucleotide reductase [15]. By interfering with Fe^{3+} uptake and utilization, gallium may inhibit viral ribonucleotide reductase activity, and thus viral replication (similar to gallium's activity against the proliferation of cancer cells and bacteria). Gallium has shown antiviral activity against human immunodeficiency virus in laboratory studies [16].

Because the neurological and biochemical mechanisms that produce PHN are not fully understood, any hypotheses regarding the amelioration of PHN by gallium remain speculative. Studies of neurons and surrounding tissue from individuals who died within a few months of having herpes zoster (though who did not die of it) suggest that

viral replication, or at least the continued presence of viral proteins, may persist in sensory ganglia long after rash resolution, causing inflammation and pain [1]. Interference with viral replication, interactions with inflammatory viral proteins, or general anti-inflammatory activity are possible means by which gallium could ameliorate PHN.

Gallium may also inhibit neuronal inflammation by acting as a mimic of zinc, thus interfering with matrix metalloproteinase (MMP) activity (MMPs are zinc-dependent proteases). The ability of gallium to inhibit MMP activity has been suggested previously [8], and has been demonstrated *in vitro* [17]. MMPs, particularly MMP-9 [18,19], MMP-2 [19], and MMP-5 [20], have been strongly implicated in the pathogenesis of neuropathic pain. Zinc is also known to modulate the secretion of the pain-associated neuropeptide substance P in afferent rat neurons [21], with high zinc concentrations strongly inhibiting the release of substance P. It is possible that gallium has a similar effect.

Limited evidence suggests that inflammation may be directly related to at least some PHN-associated pain. A randomized clinical trial found that intrathecally administered methylprednisolone (an anti-inflammatory corticosteroid) together with lidocaine was effective in relieving PHN pain (though patients with trigeminal-associated pain were not included in the study); patients receiving lidocaine alone or no treatment did not experience pain relief [22]. Interleukin-8, which is associated with neutrophil recruitment and with inflammation-associated pain, was elevated in the cerebrospinal fluid of the PHN patients, and was reduced significantly by the intrathecal methylprednisolone. These results suggest that anti-inflammatory action on neuronal tissue can, at least in some cases, relieve PHN pain.

Gallium's analgesic activity in PHN thus likely involves gallium's anti-inflammatory properties as well as other modalities. Because gallium maltolate is moderately soluble in both water and lipids (octanol : water partition coefficient of 0.41; [23]), it is expected to readily penetrate skin and neurons. Gallium maltolate thus appears particularly able to deliver gallium directly to skin, underlying tissues, and neurons when applied topically to the skin or mucus membranes.

Based on observations in the case reported here, there is justification to study topical gallium maltolate in other patients with refractory peripheral neuropathic pain. Laboratory research on the analgesic properties of gallium may elucidate its mechanisms of action; complementarily, such studies may open up new avenues of studying pain and could reveal new pain pathways.

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