Medical Hypotheses (2005) **65,** 1136—1141

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medical hypotheses

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Elimination of arthritis pain and inflammation for over 2 years with a single 90 min, topical 14% gallium nitrate treatment: Case reports and review of actions of gallium III

George Eby *

George Eby Research, 14909-C Fitzhugh Road, Austin, TX 78736, United States

Received 26 June 2005; accepted 28 June 2005

Summary Arthritis is inflammation in a joint often with joint damage, usually accompanied by pain, swelling and stiffness, resulting from infection, trauma, degenerative changes, metabolic disturbances, autoimmune or other causes. It occurs in various forms, including rheumatoid arthritis, osteoarthritis, bacterial arthritis and gout. Gallium III can inhibit the production of inflammatory cytokines, such as IL-1beta, produced by macrophage-like cells in vitro. A dose-dependent inhibition of IL-1beta and TPA stimulated MMP activity by gallium nitrate at increasing concentrations occurs, demonstrating that gallium nitrate can be a useful modulator of inflammation in arthritis. Gallium III is an inhibitor of bone resorption and is an effective treatment for hypercalcemia. Gallium III has been reported to be effective in the treatment of mycobacterium butycicum-induced arthritis in rats by antagonism of iron III. Long-term elimination of pain from arthritis by gallium III was first observed in horses primarily being treated for navicular disease. Several people treating their horses with gallium nitrate coincidentally found that arthritis pain in their fingers ended and did not return after soaking their hands in 14% gallium nitrate solution. Therefore, the severely arthritic hands of a 60-year-old woman were topically treated with a 14% aqueous solution of gallium nitrate for 90 min. Pain and inflammation from rheumatoid arthritis diminished rapidly, and neither pain nor inflammation returned during the following 2 years from that single treatment. A 61-year-old woman who had osteoarthritis in her left knee, shoulders and wrists was treated orally with 50 ml of a 1% gallium nitrate solution (120 mg elemental gallium) daily using a two week on and two week off protocol, resulting in almost total elimination of pain while on gallium nitrate, while pain partially returned during the two week off periods. Treatment of frozen shoulder with topical 40% gallium nitrate for 120 min resulted in greatly reduced pain and crepitus almost immediately with complete restoration of range of motion, with pain remaining essentially absent for over 1 year. Mechanisms of action are hypothesized to include anti-inflammatory, bone density improvements, antibacterial, anti-iron III and anti-aluminum III effects. Proper use of gallium III may be effective in terminating pain and inflammation of arthritis for years, often with a single treatment.

* Tel.: +1 512 263 6968; fax: +1 512 263 0805.
E-mail address: george.eby@coldcure.com.

0306-9877/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.mehy.2005.06.021

Introduction

Arthritis is inflammation in a joint often with joint damage, usually accompanied by pain, swelling and stiffness, resulting from infection, trauma, degenerative changes, metabolic disturbances, autoimmune or other causes. Many kinds of arthritis exist, including rheumatoid, osteoarthritis, bacterial and gout. In its various forms, arthritis has been shown to disable more people than any other chronic disorder. Arthritis can be brought about by nerve impairment, increased or decreased function of the endocrine glands, or degeneration due to age. Less frequently, it is caused by infection (tuberculosis, gonorrhea, Lyme disease, rheumatic fever). Symptomatic treatment includes use of heat, physical therapy, and nonsteroidal anti-inflammatory drugs. Remission of arthritis symptoms can sometimes be achieved with methotrexate, gold salts, penicillamine, and cortisone, but most treatments have undesirable to serious side effects. Orthopedic surgery, including artificial joint implantation, may be performed in severe cases.

Gallium III has been used for over 20 years to prevent loss of calcium from human bone from hypercalcemia, osteopenia, osteoporosis, Paget's disease, bone destruction due to metastasis from malignant tumors, and hyperparathyroidism [1]. Gallium III is a potent inhibitor of bone resorption that acts to maintain and restore bone mass in all vertebrate species. Gallium was shown by Matkovic et al. [2] in 1991 to prevent adjuvant arthritis induced by mycobacterium butycicum in rats. They showed from rotobar tests that arthritic rats treated with gallium nitrate had vastly increased flexibility of joints compared with arthritic rats not treated (409 s versus 25 s, $p < 0.0014$), and that performance of arthritic rats treated with gallium nitrate was essentially equivalent to performance of non-arthritic rats (409 s versus 422 s).

Apseloff et al. [3], in 1997 demonstrated that gallium nitrate suppresses lupus in mice. Panagakos et al., in 2000 showed that gallium III inhibits the production of inflammatory cytokines, such as interleukin-1 beta (IL-1 beta), produced by macrophage-like cells in vitro by examining its effects on matrix metalloproteinase (MMP) activity. A dose-dependent inhibition of IL-1 beta and tissue-type plasminogen activator (tPA) stimulated MMP activity by gallium nitrate at increasing concentrations was observed, demonstrating that gallium nitrate can be a useful modulator of inflammation in arthritis [4]. Since gallium III has antibacterial, anti-inflammatory activity and bone resorption inhibition activity, it may be a good candidate for treating arthritic conditions in both humans and animals.

Long term elimination of pain from arthritis by gallium III was first observed in horses primarily being treated for navicular disease. Several people treating their horses with gallium nitrate coincidentally found that arthritis pain in their fingers ended and did not return upon keeping their hands wet with 14% gallium nitrate solutions for extended periods of time with relief lasting, in one case, over 5 years. Upon noting these serendipitous effects, occasion arose to test topical and oral gallium nitrate in a small number of people who had tried many arthritis medications, and had rejected them as being either ineffective or unsafe, and who were willing to experiment with anything that might help their pain. After explaining the oral and topical treatment in horses reports, the anecdotal human observations, the efficacy and safety of IV gallium nitrate in clinical settings, the following treatments were agreed to by the patients and were conducted.

Materials and methods

One half liter bottles of 14% gallium nitrate (3.4% w/w gallium at 99.9995% purity) aqueous solutions were provided by Recapture Metals Inc., Blanding, Utah, USA, and were used either as manufactured, or were diluted with water to a 1% solution, or were concentrated to a 40% solution.

The hands of an unhealthy 60-year-old woman suffering from rheumatoid arthritis in her finger joints with severe, unremitting pain and inflammation were treated topically using 14% gallium nitrate solutions. The solution was placed in a bowl, and both hands were held in the solution, with coincidental hand wringing, for 90 min.

A 61-year-old, 75 kg woman had severe, extremely painful osteoarthritis in her left knee. She also had moderately severe pain from osteoarthritis in both shoulders and both wrists, which was aggravated by the regular use of a walker for 8 years. She was treated orally with 50 ml of a 1% gallium nitrate (120 mg elemental gallium) solution daily on a two week on and two week off protocol for a 4-month period.

To treat frozen shoulder in an otherwise healthy male, the left shoulder, shoulder blade, chest, underarm and upper arm of a 63-year-old man was topically treated with a 40% gallium nitrate solution, allowing the solution to remain on the skin until it was absorbed in 2 h.

Results

The 60-year-old woman noticed lessening of hand pain and inflammation during a 90-min soak, which continued to decrease to complete absence of pain and inflammation within 48 h. Pain and inflammation from rheumatoid arthritis did not return from that single treatment during a 2-year observation period, although bone and joint damage from the arthritis process was essentially unaffected, and both hands remained nearly useless due to muscle atrophy and ill health from pulmonary fibrosis caused by systemic scleroderma preceding and during that period.

The 61-year-old arthritic woman found that by taking gallium nitrate orally, pain was almost totally eradicated while on gallium nitrate, while the pain returned somewhat during the two week off periods. Gallium nitrate was discontinued due to knee replacement surgery. Bone density was found to be increased after the 4-month gallium nitrate treatment.

Treatment of frozen shoulder with topical 40% gallium nitrate resulted in greatly reduced pain and crepitus, and complete restoration of movement within two days. Re-treatment was required daily for several weeks to achieve nearly complete pain relief, which remained essentially absent thereafter for over 1 year, although re-treatments were occasionally required.

On occasion, gallium nitrate solutions produced a stinging sensation on the skin reminiscent of alcohol in an abrasion or cut. The stinging sensation was either ignored or rubbed by hand for relief, and the gallium nitrate was not removed.

Discussion

Based upon the reliability of the gallium nitrate for navicular disease results, and various following anecdotes of very long lasting relief from pain of arthritis, these three human observations help predict the effect of gallium nitrate treatment in arthritis.

Prior to the navicular disease research, oral or topical gallium nitrate had not been used in any specie to treat any disease. Oral gallium nitrate is effective in treating lameness in horses with navicular disease (unpublished data). See http://cold-cure.com/html/nav.html for details. Another inhibitor of bone resorption, tiludronate, a bisphosphonate, has been used effectively to treat navicular disease in horses [5]. Gallium nitrate is at least as effective as tiludronate in restoring soundness. Similarly, several horses with arthritis of the knees or hocks treated with one-half liter of 1% gallium nitrate on their feed for 14 consecutive days became sound, and lameness did not return during a 1-year observation period. The main side effect of treatment in horses was over exuberant behavior upon turnout, which was interpreted as joy from being pain-free.

Positively charged, trivalent aluminum (III) ions are an important, generally unrecognized cause of bone resorption and osteomalacia; and in particular, they are the cause of much surface bone loss. This change occurs in all mature vertebrates not associated with Vitamin D deficiency. Aluminum (III) in bone causes bone pain and proximal myopathy in all vertebrate species tested [6,7], which might cause or increase inflammation and pain in both arthritis and navicular disease. Aluminum (III) environmental contamination, mainly from leaching aluminum from soil and rocks by acid rain, has steadily increased over the last 100 years, which is coincident with the increase in the incidence rate of arthritis and navicular disease.

Horses with navicular disease treated with gallium nitrate do not respond well to gallium nitrate treatment if they have aluminum shoes with steel nails (a battery in acidic footing), presumably due to galvanic movement of Aluminum III from the shoe into the foot, while they respond well once the aluminum shoes are removed and either steel shoes or no shoes are used. This may reflect both the aggravating influence of aluminum (III), whose pro-oxidative role is well known [8,9] in arthritis pain, and the alleviating effect of gallium (III) which, when sufficiently concentrated in tissues, may well compete not only with aluminum (III) but also with iron (III), in a manner reminiscent of zinc in antagonizing iron- and/or copper-mediated hydroxyl radical production.

The anti-inflammatory and anti-edema properties of gallium III have not been systematically explored. However, the beneficial effect of a 1-h rub of topical 14% gallium nitrate solutions on trauma-induced swelling and edema in legs of both horses and humans is profound and extremely rapid, requiring hours rather than weeks for resolution. The beneficial effect of a 1-min topical rub of 14% gallium nitrate solutions on inflamed skin from insect stings is similarly rapid. Twenty-five cc of the 1% solution on the morning and evening feed of a 100 pound dog nearly eliminated his coughing and gagging from chronic bronchitis. Apselloff et al. [10] showed in 1996 that gallium nitrate ameliorated another inflammatory condition, asthma, in mice.

Over 100 types of bacteria, including tuberculosis, have been identified in arthritis. Olakanmi

et al. [11] showed in 2000 that gallium disrupts iron III metabolism of several mycobacterias, including Mycobacterium tuberculosis, within human macrophages. A strong concentration-dependent growth inhibition was observed in the presence of gallium nitrate, suggesting that gallium nitrate may have extensive, strong antibiotic properties because of its ability to substitute for iron III in bacteria, killing those bacteria.

In terms of practical application of gallium in treating bacterial infections in the field, treatment resistant acne, pimples, boils, carbuncles, folliculitis in humans, and lameness from sole abscesses in horses routinely disappear within 48 h after a single topical 10-min treatment using 14% gallium nitrate solutions. A few drops of an ophthalmic preparation of a 1% gallium nitrate isotonic saline solution used each several hours for a day terminated overnight two treatment-resistant bacterial eye infections in a human, although minor eye pain resulted from treatment due to the nitrate moiety. The antibacterial effects of gallium III have not been systematically explored, but they appear broad and useful, and are hypothesized to be beneficial in the treatment of bacteria-induced arthritis in humans and animals.

In prehistory hundreds of millions of years ago while human and animal genetics were in early development, gallium III may have been more prevalent, competing beneficially against aluminum III and iron III, and it may have been a required nutrient for all vertebrate species. Gallium is now rare in nature and essentially absent in the food supply while iron and aluminum are abundant. It is therefore hypothesized that dietary deficiencies of gallium cause mineral imbalances in these trivalent minerals resulting in arthritis, navicular disease and perhaps Alzheimer's disease.

Aqueous gallium nitrate solutions produce highly ionized species of gallium III at pH 0 (pH zero), which readily soak into skin painlessly and with neither injury, sequela nor side effects, contrary to expectations considering pH alone. Frozen shoulder was more responsive to topical 40% gallium nitrate than to 14% gallium nitrate. Gallium nitrate aqueous solutions at 40% concentrations feel oily on skin, and readily disappear into skin without any apparent injury. A mild stinging sensation, akin to alcohol in an abrasion or cut (which may feel painful to others), often occurred from topical 7% to 40% gallium nitrate application.

Crystalline gallium nitrate is both hazardous and harmful, being: (1) a potent oxidizer whose heat of reaction with reducing agents or combustibles (such as glycerin and cellulose) may cause autoignition or explosion, (2) highly corrosive to aluminum metal, and (3) injurious to skin and mucous membranes due to traces of free nitric acid. The ability of gallium III to replace aluminum III, and also of iron III, in biological species is hypothesized to have great value in treating bone/join disorders of a wide variety, especially arthritis and bursitis.

Although 40% solutions are more effective topically in the treatment of arthritis, they are illegal to ship in commerce under both United States Department Of Transportation regulations and international shipping laws and regulations unless they are shipped as ''hazardous materials'' due to their corrosive and oxidizer properties. On the other hand, the 14% gallium nitrate solutions are exempt under United States and international shipping regulations per International Air Transport Association regulations special provisions A65. Gallium is incompatible with other metals and most chemicals, and gallium nitrate must be stored only in high density polyethylene bottles.

Gallium nitrate is reminiscent of corticosteroids in its anti-inflammatory properties, but with important differences. Corticosteroids, such as predisone, suppress all immune system cells in general, which increases risk of infection. On the other hand, gallium III has a targeted effect on abnormally activated immune cells, such as macrophage, and abnormal interactions between immune cells, such as macrophage and T cells, but it does not produce an overall suppression of the immune system [1]. Also, corticosteroids cause calcium loss from bones, while gallium nitrate restores bone calcium and is an effective treatment for hypercalcemia.

In 9 years of treatment of navicular disease and/or arthritis in over 100 horses using more than 25,000 daily doses of oral gallium nitrate, no side effects or sequela have been reported due to oral gallium nitrate treatment at the dosages used. Only one mare was given oral gallium nitrate before conception and while pregnant. She delivered a normal, healthy, quiet foal, suggesting lack of toxicity during gestation and lactation. T-cell count was slightly low in several ponies using the full-sized horse dosage without evident disease or other side effects resulting. Alterations of intestinal flora, perhaps beneficial, should be anticipated in all species from oral use gallium III. Gallium III is reported to ameliorate hepatocellular injury and protect against necrosis in murine models of septic shock and hepatitis [12,13]. In open field use over a 9-year period, there have been no reports of hepatic injury in horses attributable to gallium nitrate. Radioactive gallium-67 scans have long been used in locating bacterially infected, cancerous and inflamed tissues, and gallium III's property to localize

only in these tissues is of extreme importance in the therapeutic use of gallium III.

According to Bernstein [14], the dominant mechanism underlying most of gallium's diverse activities is its ability to act as a chemically irreducible ferric iron analog in a wide variety of systems. At appropriate dosages and concentrations, and in various animal models including humans in some cases, gallium has many demonstrable and beneficial effects. Gallium beneficially affects bone resorption and formation, inhibits osteoclastic bone resorption, increases Type I collagen production, inhibits excessive parathyroid hormone secretion, inhibits secretion of interleukin 6 (IL-6) and other bone resorption-promoting cytokines by osteoblasts, osteoclasts, and their bone marrow progenitors. Gallium modulates immune activity and concentrates at sites of both inflammation and infection. Gallium: binds to lactoferrin, is concentrated by neutrophils and lymphocytes, may be taken up by macrophages and stored in ferritin, up taken by bacteria, suppresses T cell activation and proliferation without cytotocity, inhibits production of interferon gamma, suppresses development of T cell-mediated disease in animal models of rheumatoid arthritis and multiple sclerosis, suppresses uveitis, suppresses type I diabetes, suppresses macrophage activation, inhibits secretion of IL-6, suppresses tumor necrosis factor-alpha and nitric oxide by murine macrophage-like cells, suppresses rejection of allografts, suppresses severe graft versus host disease, suppresses acute tissue rejection in mice that received cardiac allografts, suppresses certain allergic responses, antimitotic to some leukocytes and macrophages, accumulates in malignant tissue, is antineoplastic in lymphatic and urothelial cancers, can inhibit DNA synthesis through substitution of Gallium III for iron III, can interfere with iron III absorption and metabolism of proliferating cells, may inhibit intracellular release of iron from iron-transferrin ultimately resulting in prevention of cell division and possibly in cell death, inhibits protein tyrosine phosphatases in human T cell leukemia cells and some human colon cancer cells, inhibits proliferation of human keratinocytes, induces apoptosis in some leukemia cell lines, induces apoptosis in human keratinocytes, is antimitotic in HeLa cells and induces probable apoptosis by cellular iron deprivation and inhibits proliferation of some infectious microorganisms including those causing syphilis, trypanosomiasis, and tuberculosis by disrupting iron III metabolism.

High dose daily oral gallium nitrate treatment in humans may not have been given outside of the case-history above, a single 14-day trial of 7.0 ml of 14% gallium nitrate solution in a well 64-year-old, 80-kg male, and a similar trial in a 50-year-old woman. It was diluted into 3.5 l of water daily for palatability and hydration. Aside from astonishingly astringent mouth-feel, treatment was essentially uneventful. Normal liver function and blood profiles on the 14th day of gallium treatment in the male were clinically demonstrated. Although intravenous administration of gallium nitrate is associated with kidney injury, which is readily reversible through re-hydration, there have been no instances reported of kidney injury in horses fed daily one half-liter of 1% gallium nitrate solutions on their feed. Concerns about excessive nitrate intake in humans (which do not make their own vitamin C) may limit oral use oral use of gallium nitrate solutions in humans.

Judging from Results above, other anecdotes above and horse data for both arthritis and navicular disease, it is hypothesized that gallium III will be shown clinically effective in terminating for multi-year periods pain and inflammation of some types of arthritis such as rheumatoid arthritis, with none of the side effects so prevalent using today's arthritis medications. However, it remains very difficult to understand how a single gallium nitrate treatment could have a multi-year anti-inflammatory effect, unless iron-dependent bacteria are involved, an elevated synovial iron deposition occurs [15], or a long-lasting gallium-induced action occurs.

The mouth-feel problem of oral gallium III, plus the toxicity and hazard of crystalline gallium nitrate due to the nitrate moiety absolutely precludes its use in pill form. Perhaps gallium citrate or an amino acid compound of gallium would be safe and effective in pill form, but the risk of kidney injury through dehydration may remain unless adequate water is consumed.

Much more research is needed, using topical and oral gallium nitrate solutions to treat various kinds of arthritis. In the United States, oral use gallium could be considered as ''dietary supplements'' under Dietary Supplement Health Education Act of 1994 (DSHEA) or as a drug. However, marketing nutrients to treat, cure, diagnose and prevent diseases is essentially illegal under the overly broad DSHEA. Gallium compounds were patented for treating arthritis in US Patent # 5,175,006 to Matkovic et al. in 1992. It is hypothesized that some kinds of arthritis are caused by gallium dietary deficiencies, and that gallium is curative.

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