Medical Hypotheses (2008) **71,** 584–590

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medical hypotheses

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A hypothesis for anti-nanobacteria effects of gallium with observations from treating kidney disease

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Received 18 April 2008; accepted 27 April 2008

Summary Nanobacteria, 100-fold smaller than common bacteria, have been purported to exist in urine, and by precipitating calcium and other minerals into carbonate apatite around themselves, induce the formation of surrounding kidney stones. Nanobacteria-like structures have also been shown in blood, within arteries, aortic aneurysms, and cardiac valves. Gallium has antibiotic properties to iron-dependent bacteria and has potent anti-inflammatory, anticancer and anti-hypercalcemic properties, and it readily reverses osteoporosis. It was hypothesized that gallium nitrate might have benefit in treating kidney stones. Gallium nitrate (120 mg gallium) was mixed with water making two liters of a gallium mineral water drink to treat chronic, treatment-resistant kidney stone pain and urinary tract bleeding in a 110 pound woman. On the third day of gallium mineral water treatment, the urine appeared snow white, thick (rope-like) and suggestive of a calcific crystalline nature. After release of the white urine, the urine returned to normal in color, viscosity and pH, kidney pain was no longer present, and there was no further evidence of blood in the urine. There were no treatment side effects or sequela. For a one year observation period thereafter, no kidney stones, white urine, kidney or urinary tract pain or blood in the urine was noted. The hypothetical susceptibility of nanobacteria to gallium treatment also suggests application to atherosclerosis and other diseases. Although some support for gallium in treating kidney stones is presented, this hypothesis is built upon another hypothesis, is extremely speculative, and alternative explanations for the white urine exist. Further research into gallium's effects on kidney disease and other nanobacteria-induced diseases such as cardiovascular diseases is suggested.

Introduction

Nanobacteria are the smallest cell-walled bacteria (200–500 nm in diameter – 100-fold smaller than common bacteria) discovered in human and animal blood, commercial cell culture serums and vaccines. In 1997, Kajander and Çiftçioglu [1] in Finland first reported the nanobacteria explanation for kidney stone formation. They showed that all growth phases of nanobacteria produce biogenic carbonate apatite on their cell envelope. The biomineralization from living nanobacteria in cell culture media resulted in white biofilms and mineral aggregates closely resembling those found in tissue

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0306-9877/$ - see front matter
doi:10.1016/j.mehy.2008.04.025

calcification and kidney stones. The overall composition of biofilm and solid mineral formation was shown similar to that of bone, except carbonate apatite was formed, as in most extraskeletal tissue calcification and stones, whereas in bone, hydroxyapatite is the prevalent form. According to Kajander and Çiftçioglu, living nanobacteria formed carbonate apatite at pH 7.4, at physiological phosphate and calcium concentrations and produced apatite in media mimicking tissue fluids and glomerular filtrate. Apatite was suggested to play a key role in the formation of all kidney stones. Çiftçioglu et al. [2] in 1998 showed that in 97.2% of all human kidney stones tested, nanobacteria were found, and that they reliably produced apatite stones *in vitro*. They showed that nanobacteria lived in urine, and by precipitating calcium, phosphates and other minerals into carbonate apatite around themselves, induced the formation of surrounding kidney stones. Çiftçioglu et al. [3] in 2002 showed that tetracycline, some other antibiotics and the bisphosphonates, specifically etidronate and clodronate, were cidal to nanobacteria and they were shown to block aggregation, growth and mineralization of these crystals. These self-replicating, nanoparticles (*Nanobacterium sanguineum*) were also shown to be found in blood and in atherosclerotic plaques.

Trivalent gallium is also known to have antibiotic properties to iron-dependent bacteria, but it has not been tested *in vitro* against nanobacteria. Most recently, Harrington et al. [4] in 2006 reported that Gallium(III) kills *Rhodococcus equi*, an intracellular bacteria, which causes pneumonia in foals. The extensive review of Bernstein [5] showed that gallium was effective in treating experimental syphilis in rabbits, eliminated *Trypanosoma evansi* parasites from infected mice, killed *Mycobacterium tuberculosis* and *Mycobacterium avium* complex and was effective against malarial parasites. Bernstein suggested that it is likely that the activity stems from gallium's ability to enter microbes through their iron transport mechanisms, to disrupt their iron metabolism, and to interfere with protein synthesis. The ability of transferrin-bound gallium to enter infected cells through the transferrin receptor may be an advantage in treating some intracellular infections. Other bacterial infections are treatable with gallium nitrate. Eby [6] reported that a single topical application of a gallium nitrate solution was immediately effective in terminating pimples, acne, boils, folliculitis and carbuncles and other bacterial skin infections. Eby also reported that a 1% gallium nitrate isotonic saline ocular solution used each several hours for a day terminated overnight two treatment-resistant bacterial eye infections in humans. In 2007, Kaneko et al. [7] found that gallium inhibits *Pseudomonas aeruginosa* growth and biofilm formation and kills planktonic and biofilm bacteria *in vitro*. The antibacterial effects of gallium have not been systematically explored, but they appear broad, safe and useful.

Warrell [8] in 1995 showed that gallium also has actions significantly superior to etidronate in terminating cancer-induced hypercalcemia, reversing osteoporosis. Extensive research over the years using gallium to treat hypercalcemia has been conducted. Eby [6] in 2005 suggested that gallium nitrate was effective in treating arthritis, and more effective than etidronate in treating several other arthroses, including navicular disease and navicular syndrome, in horses. Gallium nitrate has been used for many years to treat osteoporosis by the IV route in hospitalized patients as reported by Warrell and others, and by the oral route mentioned by Eby during the treatment of arthritis.

It is hypothesized that gallium would have benefit in treating kidney stones because it has actions similar and superior to etidronate in that they are both beneficial in restoring bone mass by removing calcium from the blood and both have antibacterial properties. Since etidronate was effective in killing nanobacteria [3], it is hypothesized that gallium nitrate also would be cidal to nanobacteria. After discussing the possible benefits and apparent lack of side effects of gallium nitrate at dosage contemplated with a subject with kidney stone pain, and after informed consent was obtained, the following otherwise healthy subject tested gallium nitrate for efficacy in treating kidney stone pain.

Materials and methods

One half liter bottles of 14% gallium nitrate (3.4% w/w gallium at 99.995% purity) aqueous solutions were provided by Recapture Metals Inc., Blanding, Utah, USA. Three and one-half milliliters of the 14% solution (120 mg elemental gallium) were mixed with 2 l water to prepare a gallium mineral water drink, which had an astringent mouth-feel.

Drinking the gallium mineral water was an attempt to treat chronic kidney stone pain and urinary tract pain in a 110 pound female nurse. She had not shown kidney stones upon X-ray examination, but remained totally convinced that she had ''kidney stones'', since she could feel their passage and hear them striking the toilet bowl. The kidney stone pains had begun 5 years previously after contracting a life-threatening bacterial infection while working in a hospital as a nurse. Kidney stone pain

and urinary tract pain and bleeding occurred every day during those 5 years, and pain was constant and severe, consistent with kidney stone pain. Multiple urine tests during those 5 years failed to show any evidence of urinary tract infection, although tests for nanobacteria were not performed. She had undergone many treatments during that 5-year period without benefit for her kidney disease, and gallium treatment seemed to her to be her last chance for recovery. The gallium mineral water was consumed in a split-dose manner as a source of drinking water each day for three days.

Results

On the third day of gallium treatment, the urine, previously clear and otherwise normal, appeared snow white and thick (rope-like). Kidney pain ceased and blood in the urine was no longer evident. The pH of the white urine was 8.5, and together with the white color, such were suggestive of large amounts of calcium or other alkaline minerals. No further chemistry was performed and the white urine was discarded. On following days, the urine was normal in color, was normal in viscosity, had a normal pH, and showed no visible evidence of excess minerals or kidney disease in general. There were no side effects and no sequela occurred. For a one year post-treatment observation period, no stones, kidney or urinary tract pain or blood in the urine was noted and overall health remained normal. Stones and pain reappeared after one year absence and were again successfully treated with gallium nitrate.

Discussion

The effect of gallium nitrate in treating kidney disease by solublizing kidney stones, possibly formed by nanobacteria, appeared evident in this case; however, since no further chemistry was performed, other possibilities such as pus, lymph and uric acid crystals must also be considered. Regardless, after three days of oral gallium nitrate treatment of her kidney disease, what is hypothesized to have been carbonate apatite of kidney stones visibly appeared in the urine as a white, highly viscous liquid. Another woman with severe, constant kidney pain, believed to have been of an infectious nature, also used gallium nitrate treatment to eliminate kidney pain in less than 2 days. These observations appear similar or identical to the observations of Krakoff et al. [9] in 1979, who showed bursts of urinary calcium excretion upon IV administration of 750 mg gallium nitrate per meter squared in the treatment of advanced human cancer, which was also reported to have occurred in the rat under similar circumstances, showing a close association of gallium with calcium and phosphate in the occluding renal tubular precipitate.

Alternative hypotheses such as that of Cisar et al. [10] for the biomineralization in kidney stones should also be considered. However, the main role of Gallium(III) is antibiotic in nature, specifically where the bacteria are iron-dependent since Gallium(III) irreversibly displaces Iron(III) in them, rapidly killing them. Thus, this observation of gallium nitrate terminating kidney pain, perhaps by dissolving many tiny kidney stones or tiny abrasive and sharp crystals, mainly supports the finding of Kajander and Çiftçioglu [1]. It is hypothesized that living nanobacteria are killed by gallium nitrate with the result being a disassociation of their calcium shells producing white, nanometer-sized particles with some dissolved calcium, with both immediately flowing out of the kidneys and into the urine in a painless and highly visible manner.

The significance of nanobacteria extends beyond kidney stones to include a variety of disorders including atherosclerosis, cancer and arthritis because unexplained calcium precipitation, chemically similar to kidney stones, occurs in various tissues of the body in these diseases.

Concerning atherosclerosis, Rasmussen et al. [11] in 2002 provided electron microscopic and immunological evidence of nanobacteria-like structures in calcified carotid arteries, aortic aneurysms, and cardiac valves. Miller et al. [12] in 2004 showed evidence of nanobacteria in calcified human arteries and cardiac valves. Nadra et al. [13] in 2005 showed that basic calcium phosphate crystal deposition underlies the development of arterial calcification. Inflammatory macrophages colocalize with crystal deposits in developing atherosclerotic lesions, and *in vitro* can promote calcification through the release of TNFα. This was associated with secretion of pro-inflammatory cytokines (TNFα, IL-1β and IL-8) capable of activating cultured endothelial cells and promoting capture of flowing leukocytes under shear flow. The presence of arterial calcification has been viewed as a passive bystander phenomenon and as a useful clinical marker of progression of atherosclerotic disease. However, Nadra [13] has clearly demonstrated an active inflammatory response by macrophages to calcified crystals in arteries. The response of macrophages to these crystals shows that pathological calcification is not merely a passive consequence of chronic inflammatory disease, but leads to a positive feed-back loop of calcification and inflammation driving disease progression

forward. Maniscalco and Taylor [14] in 2004 combined EDTA with tetracycline and nutrients and showed a 14% decrease in coronary artery calcium scores over a 4 month period while angina was decreased or abated in 84% of their patients. Supporting the potential future role of gallium in treating atherosclerosis, Makkonen et al. [15] in 1995 showed that gallium greatly inhibited the release of TNFα from activated macrophages, and Panagakos et al. [16] in 2000 showed that gallium greatly inhibited the cytokine IL-1β. It is hypothesized that gallium nitrate, also an antibiotic, will reduce these inflammatory mediators and disassociate calcified atherosclerotic lesions in much the same manner that gallium nitrate is hypothesized to disassociate calcium shells around nanobacteria in kidney stones, thus inflammation induced by the crystals should also terminate, ending atherosclerosis. Nanobacteria may cause ''hardening of the arteries'' and it is hypothesized that gallium is the antidote.

Concerning cancer, gallium is the only mineral other than platinum to have frequently demonstrated, strong anticancer properties, although Eby [17] and others have suggested beneficial effects of zinc in treating childhood leukemia. Chua et al. [18] in 2006 reported that gallium maltolate was a promising chemotherapeutic agent for the treatment of hepatocellular carcinoma (HCC). The ability of tumors to accumulate gallium, while normal tissue do not accumulate it, results in highly preferential anti-proliferative targeting, with normal tissues being spared. The avidity of even distant metastases for gallium raises the possibility of the first potential treatment for metastatic HCC. Chua et al. also cited some of the anticancer properties of gallium to non-Hodgkin's lymphoma, murine leukemic L1210 cells, human leukemic HL60 cells, MCF-7 and HELA cells, brain tumor cells, human leukemic CCRF-CEM cells, human breast cancer MCF-7 cell line, the 13762NF rat mammary adenocarcinoma, mantle cell lymphoma, human leukemic HL60 cells. Other cancer cell lines are also susceptible to gallium and include Walker 256 carcinosarcoma [19], and Lewis lung tumors in mice [20], bladder and lymphomas [21]. The anti-proliferative effect of gallium is again likely related to its competition with iron [22], and gallium modifies three-dimensional structure of DNA and inhibits its synthesis, modulates protein synthesis, inhibits the activity of a number of enzymes, such as ATPases, DNA polymerases, ribonucleotide reductase and tyrosine-specific protein phosphatase. Gallium alters plasma membrane permeability and mitochondrial functions. Collery et al. [23] in their 2002 comprehensive review of gallium in cancer therapy, showed that oral-use gallium compounds are taken up more efficiently (relative to intravenous administration) and more specifically by tumor cells with much less toxicity, and that considerably higher doses than used in this test are possible. Consistent with the hypothesis that excess iron with excess calcium promotes cancer, such is supported according to epidemiology research for lung cancer [24], gallium should be beneficial in its treatment. Although gallium has been shown effective in some cancers, not all are susceptible to gallium treatment.

Concerning arthritis, nanobacteria-like particles have been shown to exist in synovial fluids of both rheumatoid arthritis and osteoarthritis patients [25]. Eby [6] in 2005 suggested the ability of 1% oral-use gallium nitrate solutions and 14—42% topical use gallium nitrate solutions to terminate arthritis rapidly and permanently in both humans and horses, and the bactericidal effects of Gallium-III may have been responsible for such rapid and permanent action. Gallium can also inhibit the production of inflammatory cytokines in arthritis, such as IL-1β, produced by macrophage-like cells *in vitro*. A dose-dependent inhibition of IL-1β 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 is an inhibitor of bone resorption and is an effective treatment for hypercalcemia. Gallium has been reported to be effective in the treatment of mycobacterium butycicum-induced arthritis in rats by antagonism of iron.

Radioactive gallium scans take advantage of the property of gallium to accumulate only in inflamed, infected and cancerous tissues, suggesting which tissues would be subject to intense treatment with Gallium-III.

The beneficial effects of gallium in the treatment of kidney stone pain, cancer and arthritis have been demonstrated to varying degrees, and benefits are believed to result from its action on iron, inflammation and bacteria. Hypothetically, coronary artery inflammation caused by calcification results from simple mechanical injury by the hard, sharp crystals, and their removal by gallium is hypothesized to terminate coronary artery disease. For reasons described herein, it is hypothesized that gallium might be beneficial in the treatment of atherosclerosis, likely producing a 4-day response to treatment like the case shown here for kidney stone pain. There is substantial concern about large amounts of free calcific nanoparticles loose in the blood and what they might do to kidneys and the brain as well as the arteries. Polymer

nanoparticles more than 5 nm in size have been experimentally used to transport cancer drugs such as methotrexate, and those particles appear to pass freely through the kidneys of mice, but not the blood-brain barrier [26]. Nanoparticles over 8 nm in diameter will reflect white light, and it is hypothesized that most calcific particles freed by gallium will be 8 nm or larger, although there is also likelihood of dissolved calcium. Rapid blood increases in free calcium may precipitate temporary, clinical depression [27].

The hypothetical effects of gallium in the treatment of atherosclerosis remain to be demonstrated. It is cautiously hypothesized, and totally unproven and undemonstrated in any manner, that appropriate dosages of gallium mineral water might beneficially treat ''hardening of the arteries''. Concerning safety and side effects of long-term gallium nitrate treatments, some horses have been treated for navicular disease with large amounts of gallium nitrate as a safe anti-inflammatory agent without immune system injury daily for over 12 years with no indication of any adverse side effects or sequela [28], and gallium nitrate has a long history of use in humans.

Perhaps the most important question is how much oral gallium should be administered in treating atherosclerosis and kidney stones without the risk of side effects. The answer is unknown at this time, although some people, not being treated directly for atherosclerosis — but of an age group likely to have atherosclerosis — have taken 120—240 mg of oral gallium (as gallium nitrate) daily for several months without evident side effects in the treatment of arthritis [6]. On several occasions much larger oral doses were taken, with one case ten times larger resulting in diarrhea without further sequela. The LD_{50} oral dose for mice of gallium nitrate is 2.15 g per kilogram (equivalent to 0.59 g per kilogram elemental gallium). Ten milligrams per kilogram oral dose produced no visible toxicity in dogs despite monitoring bone marrow, kidneys and liver. Oral daily doses of 200—400 mg per kilogram of gallium chloride for 20—40 days in rats and mice induced no visible signs of toxicity [22]. Dosages and toxicity of various gallium compounds are discussed in detail by Collery et al. [23]. The mode of delivery should be oral and not intravenous, since mainlining gallium has repeatedly been shown to cause reversible kidney damage [5,8,9], requiring substantial rehydration.

Çiftçioglu et al. [29] in 2005 suggested that enhanced growth of nanobacteria during microgravity was the cause of the increased incidence of kidney stone formation during space flight. It is hypothesized and suggested that gallium mineral water (<1% gallium nitrate) be used during space flights to preserve bone density, protect the cardiovascular system and prevent kidney stones.

Gallium nitrate can not be consumed in ''pill'' form because it is extremely oxidizing and corrosive due to the nitrate moiety, and it must always be consumed mixed in large amounts of water for human and animal safety, thus the concept of a safe ''gallium mineral water'' results. Gallium, from gallium nitrate, appears positively charged [Gallium(III)] and highly ionized at physiologic pH. Although gallium combines with transferrin in the blood, the chemical nature of gallium in urine is not known to the author. Gallium nitrate crystals are sufficiently corrosive to melt through aluminum foil overnight, although 42% gallium nitrate solutions do not have such capacity. Gallium nitrate used in this test needs distinction from Ganite®, which is ''citrated'' gallium nitrate. There is some possibility that the beneficial effects of gallium nitrate on kidney stone pain and perhaps atherosclerosis would not result from neutrally or negatively charged gallium species, in the same manner that only positively charged zinc [Zinc(II)] species in throat lozenges have efficacy in treating (shortening) common colds [30]. However, since the route of administration of gallium for anti-nanobacteria effects is by the oral route and not topically, this likelihood is low.

The notion that inadequate magnesium and excessive calcium intake causes kidney stones as described by Massey [31] continues to have validity, but it is now hypothesized that nanobacteria disrupt the relationship between magnesium and calcium to produce kidney stones, cardiovascular diseases and other illnesses.

In foods, gallium is believed to be in the 10 (orange juice) to 600 (beef) nanogram per gram food range [32—34]. In United States Geological Service soil surveys of the Atlantic Coastal Plains of South Carolina (http://pubs.usgs.gov/of/2004/1368/) accessed May 14, 2006, crustal gallium was 19 mg/kg, compared with 41,500 mg/kg calcium and 23,300 mg/kg magnesium. Perhaps due to its limited availability and the hypotheses presented herein, the reason why there is such a high incidence of heart attacks in South Carolina is found. Although trace amounts of gallium are ubiquitous in nature, perhaps inadequate amounts are ingested to prevent cardiovascular diseases and other illnesses. Gallium is immediately to the right of zinc on the periodic table of elements, has an atomic number of 31 and an atomic weight of 69.723. Eby and Halcomb [35] in 2006 showed that supplemental zinc could terminate angina pectoris and Reynaud's diseases, and similarly Maniscalco

and Taylor [14] showed that their antibiotic ''cocktail'' could terminate angina. Consequently, the idea that biocidal Gallium(III) could terminate atherosclerosis has some plausibility by association. The amount of gallium in a human appears to be about one milligram. In the United States, gallium can be a dietary supplement or a drug, dependent on the application.

Conclusions

The observation of thick (rope-like) white urine after treatment of kidney pain with oral gallium nitrate mineral water resulting in essentially permanent cessation of kidney and urinary tract pain and blood in the urine could have been an important observation if the chemical and biological nature of the white urine had been established. If the white urine actually contained dissolved calcium crystals, the observation might have relevance to the treatment of atherosclerosis by gallium as a hypothetical anti-nanobacteria agent, however these conclusions must remain extremely hypothetical and highly suspect until confirming research is conducted, even though these observations are similar or identical to those of Krakoff et al. [9]. For example, the thick white urine could also have been pus, lymph or crystalline uric acid, and benefits of gallium nitrate in their treatment might not be nearly as exciting as the hypothesis presented. Regardless, gallium nitrate appeared effective and safe in treating severe, treatment resistant, chronic kidney pain with urinary tract pain believed to have been caused by stones.

Possible conflict of interest

The author sells gallium nitrate solutions for the treatment of navicular bone and joint disorders in horses at http://gallium-nitrate.com.

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