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Gallium, Therapeutic Effects

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Synonyms

Gallium and apoptosis; Gallium effect on bacteria; Gallium uptake

Definition

Gallium: Gallium is an element (atomic number 31; atomic weight 69.723) in Group XIII of the periodic table (below aluminum, above indium), classed as a semimetal or poor metal. It occurs in the Earth's crust at an average abundance of about 15–19 parts per million (ppm) (similar to the abundance of nitrogen and about ten times that of tin or arsenic), widely distributed in soils and rocks. The element is extracted mainly from bauxite (in which it occurs at an average concentration of roughly 50 ppm) as a byproduct of aluminum refining, and to a lesser extent from zinc ores.

Introduction

Gallium is not known to have any essential biological function, but it exerts a variety of therapeutically useful biological activities. Many of these activities derive from gallium's ability to act as an irreducible mimic of ferric iron (Fe^{3+}). Gallium's ability to compete with other essential metals, particularly zinc, is likely responsible for some of its other biological activities.

The ionic radii, electronegativity, ionization potentials, and coordination chemistry of Ga^{3+} are remarkably similar to those of Fe^{3+}. In the body, Ga^{3+} can be transported in the blood serum by the iron transport protein transferrin, and appears to follow many of the uptake and transport pathways observed for iron (Bernstein 1998).

It is, however, the differences between Ga^{3+} and Fe^{3+} that allow gallium to be therapeutically useful. By being irreducible under physiological conditions, gallium cannot participate in redox reactions, such as the

Fenton-type reactions that make free iron (mainly as Fe^{2+} in solution) highly toxic. Gallium also is not observed to enter Fe^{2+}-bearing molecules such as heme, and so does not interfere with oxygen transport (via hemoglobin) or with cytochrome-mediated reactions. Furthermore, at pH 7.4 and 25°C, Ga^{3+} has a solubility of about 1 μM (98.4% as $[Ga(OH)_4]^-$ and 1.6% as $Ga(OH)_3$) whereas Fe^{3+} has a solubility of only about 10^{-18} M. Thus, small amounts of nonprotein-bound gallium can exist in solution at physiological conditions, versus insignificant amounts of nonprotein-bound Fe^{3+}, permitting biological interactions for Ga^{3+} that would not be possible for Fe^{3+}.

Gallium metalloproteins: Gallium is known to substitute for iron in several human proteins. Crucial to many of gallium's activities in the body, it binds to the two metal sites on transferrin (TF). Typically, serum TF is about 33% saturated with Fe, leaving 67% available for binding by Ga (about 2.7 μg/mL). Under usual physiologic conditions, the binding constants for gallium are log $K_1 = 20.3$ and log $K_2 = 19.3$; the corresponding binding constants for Fe^{3+} are log $K_1 = 22.8$ and log $K_2 = 21.5$. However, whereas Fe^{3+} remains bound to TF down to a pH of about 5.5, Ga^{3+} starts to dissociate from TF at pH < 6.8; it is >50% dissociated at pH 6 (McGregor and Brock 1992). This difference in stability may provide a therapeutic advantage to TF-bound Ga, as it may be released sooner than Fe in endosomes of cancer cells and phagosomes of some pathogens, helping it to compete against Fe (Bernstein et al. 2011). In addition to binding to TF, gallium binds even more avidly to the related protein lactoferrin as well as to the iron storage protein ferritin.

The substitution of Ga^{3+} for Fe^{3+} is also observed in bacterial proteins, including ferric-binding protein (FbpA), an iron transporter in the same protein superfamily as TF (Weaver et al. 2008). The presence of such substitutions could inhibit bacterial growth. Ga^{3+} can also substitute for Fe^{3+} in non-ribosomal peptide microbial siderophores.

Ionic gallium is observed to dose-dependently inhibit alkaline phosphatase (Boskey et al. 1993) and matrix metalloproteinase activity (Panagakos et al. 2000). This effect is hypothesized to be caused by the substitution of gallium for zinc in these proteins. Gallium and zinc are chemically similar, with gallium found substituting for zinc in minerals (e.g., gallium was first discovered replacing zinc in sphalerite, cubic ZnS).

Therapeutic gallium compounds: Numerous gallium compounds have shown evidence of therapeutic activity (Table 1). These compounds include inorganic and organic salts, metal-organic complexes, metalloproteins, and organometallics. As with all metals and semimetals, the chemical form in which gallium occurs is crucial to its absorption, distribution, excretion, and activity. The biochemical properties of gallium are thus dependent on the chemical form in which it is delivered. Organometallic gallium compounds (having Ga–C bonds), as well as some highly stable complexes (including Ga porphyrins), tend to remain fairly intact under physiological conditions, so their molecular conformation helps determine their activity. Other compounds, such as some orally administered gallium salts and complexes, are prodrugs in that they dissociate before reaching the bloodstream, with the gallium becoming bound mainly to transferrin and other proteins. Depending on their route of administration and chemical nature, gallium compounds can undergo various degrees of metabolic alteration in the body, resulting in varying contributions from the gallium itself versus its molecular host.

Currently, the only gallium compounds reported to have been tested in humans are citrated gallium nitrate for injection (Ganite®; approved for use in the USA to treat cancer-related hypercalcemia); gallium maltolate for oral administration (Phase I trials); gallium 8-quinolinolate for oral administration (Phase I trials); and gallium chloride for oral administration (in a few cancer patients).

Therapeutic activities: The known therapeutic activities in which gallium may play a major role include: (1) Activity against pathological hyperproliferation, particularly against some aggressive cancers; (2) Anti-inflammatory and immunomodulating activity, as observed in animal models of rheumatoid arthritis, multiple sclerosis, and lupus; (3) Anti-bone-resorptive and anti-hypercalcemic activity, plus possible anabolic bone activity; (4) Activity against some pathogenic microbes, including *Pseudomonas aeruginosa* and some intracellular bacteria; and (5) Possible analgesic activity, including against neuropathic pain.

Gallium in the Treatment of Cancer

Following the discovery of cisplatin's (*cis*-diammine-dichloroplatinum(II)) anticancer activity in 1969, there

Gallium, Therapeutic Effects, Table 1 Therapeutic gallium compounds

Compound	Therapeutic activities	References
Inorganic salts and glasses		
$GaCl_3$	In vitro *and animal studies*: Anticancer, particularly in aggressive tumors; active against *Pseudomonas aeruginosa* *Human clinical studies*: Oral bioavailability low. Possible potentiation of cisplatin and etoposide therapy in lung cancer patients.	Bernstein (2005); Banin et al. (2008)
$Ga(NO_3)_3$ (In many of the in vitro and animal studies, and in all of the human clinical studies, citrate was added to solutions of gallium nitrate in order to neutralize the pH and to increase stability. The molar concentration of the citrate was generally the same as that of the Ga)	In vitro *and animal studies*: Anti-bone-resorptive; possible anabolic activity on bone; immunomodulating: effective in animal models of rheumatoid arthritis, multiple sclerosis, and others; anticancer; antimicrobial, including against *Mycobacteria*, *Pseudomonas*, *Staphylococcus*, *Francisella*, and others; antibiofilm activity *Human clinical studies*: Low oral bioavailability. Intravenous formulation approved in the USA for cancer-related hypercalcemia. High efficacy observed for Paget's disease of bone, lymphoma, multiple myeloma; low to moderate efficacy observed for urothelial carcinoma, ovarian cancer, metastatic prostate cancer	Bernstein (2005)
$Ga_2(SO_4)_3$	Suppressed adjuvant arthritis in rats	Bernstein (1998)
Ga_2O_3-doped phosphate-based glasses	Activity against *Staphylococcus aureus*, *Escherichia coli*, and *Clostridium difficile*	Valappil et al. (2008)
Organic salts and complexes		
Ga citrate	Activity against *Pseudomonas fluorescens*	Al-Aoukaty et al. (1992)
Ga tartrate	Eliminated experimental syphilis in rabbits at a single dose of 30–45 mg Ga/kg intramuscularly or 15 mg Ga/kg intravenously. Eliminated *Trypanosoma evansi* infection in mice at 225 mg/kg	Levaditi et al. (1931)
Ga maltolate (tris(3-hydroxy-2-methyl-4 H-pyran-4-onato)gallium(III))	In vitro *and animal studies*: Anticancer, including against hepatocellular carcinoma; effective in animal models of rheumatoid arthritis; antimicrobial: effective against *P. aeruginosa, Rhodococcus equi, S. aureus, Staphylococcus epidermidis* and other bacteria; antibiofilm *Human clinical studies*: Oral formulation safe in Phase I trials; anecdotal efficacy observed in hepatocellular carcinoma, metastatic colon cancer, lymphoma. Topical formulation has shown anecdotal efficacy in pain, including postherpetic neuralgia, inflammation, actinic keratosis, and psoriasis	Bernstein et al. (2000); Bernstein (2005); Chua et al. (2006)
Ga 8-quinolinolate (tris(8-quinolonato)Ga (III))	In vitro *and animal studies*: Anticancer, including against lung cancer, melanoma; anti-bone-resorptive *Human clinical studies*: Oral formulation safe in Phase I trials; possible efficacy in renal cell carcinoma.	Bernstein (2005)
Ga complex of pyridoxal isonicotinoyl hydrazone	Potently antiproliferative in T-lymphoblastic leukemic CCRF-CEM cells	Bernstein (2005)
Ga protoporphyrin IX	Activity against *Yersinia enterocolitica*, *S. aureus*, *Mycobacterium smegmatis* and others	Stojiljkovic et al. (1999); Bozja et al. (2004)
$[GaL_2]ClO_4$; L = 2,4-diiodo-6-{[(pyridin-2-ylmethyl)amino]methyl}phenol	Inhibited PC-3 prostate cancer xenographs in mice; inhibited proteosome activity	Chen et al. (2007)
Ga-deferoxamine	Active against *P. aeruginosa* in vitro and in rabbit cornea together with gentamicin	Banin et al. (2008)

(*continued*)

Gallium, Therapeutic Effects, Table 1 (continued)

Compound	Therapeutic activities	References
Ga complexes of thiosemicarbazones	Activity against several cancer cell lines; activity against *Cryptococcus*	Kowol et al. (2009); Bastos et al. (2010); Mendes et al. (2009)
$(LH)_2[GaCl_4]Cl$; L = 1-methyl-4,5-diphenylimidazole	Modest activity against several cancer cell lines	Zanias et al. (2010)
$[Ga\text{-}3\text{-}Madd]^+$, $[Ga\text{-}5\text{-}Madd]^+$, $[Ga\text{-}3\text{-}Eadd]^+$, $[Ga\text{-}3\text{-}M\text{-}5\text{-}Quadd]^{+a}$	Activity against *Plasmodium falciparum*	Sharma et al. (1997); Ocheskey et al. (2003, 2005); Harpstrite et al. (2003)
Ga complexes of pyrazoles, indazoles, and benzopyrazoles	Moderate activity against human immunodeficiency virus	Kratz et al. (1992)
Ga complexes of pyrazole-imine-phenols and pyrazole-amine-phenols	Activity against MCF-7 breast cancer and PC-3 prostate cancer cell lines	Silva et al. (2010)
Ga-curcumin	Activity against mouse lymphoma L1210 cell line	Mohammadi et al. (2005)
Diphenyl Ga chloride	Moderate activity against *Candida albicans*, *Cryptococcus neoformans*, *Bacillus subtilis*, and *S. aureus*	Srivastava et al. (1973)
Tris(*N*-methylthioacetohydroxamato) Ga(III)	Moderate activity against several species of bacteria and fungi	Abu-Dari and Mahasneh (1993)
Protein complexes		
Ga transferrin	Active against MCF-7 breast cancer and HeLa cervical carcinoma cells in vitro	Jiang et al. (2002); Head et al. (1997); Olakanmi et al. (2010)
	Active against *Francisella tularensis* and *Francisella novicida* in vitro	
Ga lactoferrin	Active against *F. tularensis* and *F. novicida* in vitro and protected against *F. novicida* nasally introduced to mice	Olakanmi et al. (2010)
Organometallics, organometallic complexes		
$[((CH_3)_2\,Ga)(5\text{-phenyl-}1,3,4\text{-oxadiazole-}2\text{-thio})]_4$	Active against several cancer cell lines	Gallego et al. (2011)
Dimeric methyl-Ga complexes of some carboxylates	Active against several cancer cell lines	Kaluđerović et al. (2010)
α-dimethylamino-cyclohexoxyl-dimethyl-gallium	Active against *P. falciparum*	Yan et al. (1991)
Miscellaneous		
Doxorubicin-Ga-transferrin conjugate	Active in vitro against MCF-7 breast cancer cells, including those resistant to doxorubicin; anecdotal efficacy in breast cancer patients	Wang et al. (2000); Bernstein (2005)
Sulfonated Ga corrole bound to a heregulin-modified protein	Active against HER-positive cancer in rats	Agadjanian et al. (2009)
Liposomal $Ga(NO_3)_3$ and gentamicin	Very active against *P. aeruginosa* biofilms	Halwani et al. (2008)
Yeast-incorporated Ga	Antiresorptive and anabolic to bone in rats	Ma and Fu (2010)

[a]$[Ga\text{-}3\text{-}Madd]^+$ = [{1,12-bis(2-hydroxy-3-methoxybenzyl)-1,5,8,12-tetraazadodecane}gallium(III)]$^+$;
$[Ga\text{-}5\text{-}Madd]^+$ = [{1,12-bis(2-hydroxy-5-methoxybenzyl)-1,5,8,12-tetraazadodecane}gallium(III)]$^+$;
$[Ga\text{-}3\text{-}Eadd]^+$ = [{1,12-bis(2-hydroxy-3-ethyl-benzyl)-1,5,8,12-tetraazadodecane}gallium(III)] $^+$;
$[Ga\text{-}3\text{-}M\text{-}5\text{-}Quadd]^+$ = [{1,12-bis(2-hydroxy-3-methoxy-5-(quinolin-3-yl)-benzyl)-1,5,8,12-tetraazadodecane}-gallium(III)]$^+$

was a systematic effort to determine the anticancer efficacy of other metal compounds. By 1971, after an initial round of in vitro and animal screening, gallium emerged as being particularly promising. Specifically, parenterally administered gallium nitrate showed efficacy in several animal cancer models, including Walker 256 ascites carcinosarcoma in rats and implanted human medulloblastoma in mice. In vitro activity of gallium compounds has been observed in a number of cancer cell lines, including those for

lymphoma (Chitambar 2010), breast cancer (Wang et al. 2000), leukemia (Bernstein 1998), and hepatocellular carcinoma (Chua et al. 2006) (see Table 1 for more examples of in vitro and in vivo anticancer activity).

The discovery of gallium's anticancer activity coincided with the introduction of ^{67}Ga-scans to diagnose and locate a variety of cancers in the body. ^{67}Ga-scans were found to be particularly sensitive to lymphomas, some sarcomas, and bone tumors, but much less sensitive to many other types of cancer. For Ga-sensitive cancers, ^{67}Ga-scans were noted to detect growing cancer tissue rather than cancer tissue that was necrotic or otherwise less active. Many of the ^{67}Ga-avid cancers soon proved to be most susceptible to therapeutic gallium treatment, though this correlation was apparently not documented or utilized.

Mechanisms of antiproliferative activity: The sensitivity of multiplying cancer cells to gallium appears due mainly to their high need for iron. This need stems primarily from the requirement for iron in the active site of ribonucleotide reductase, an enzyme essential for the synthesis of DNA. To obtain sufficient iron, most cancer cells highly overexpress TF-receptor (though some cancer cells can also take up iron by TF-receptor-independent mechanisms). If Ga is present on the available TF, the Ga-TF will be taken into the cell by endocytosis and compete with iron. Ga then hinders acidification of the TF-bearing endosome, possibly inhibiting release of Fe (which occurs at pH < 5.5). Gallium thus interferes with the uptake and utilization of iron by cancer cells; in addition, it has direct inhibitory activity on ribonucleotide reductase (Bernstein 1998). Cancer cells that are consequently unable to make DNA and multiply ultimately undergo apoptosis (see "▶ Gallium Nitrate, Apoptotic Effects" for further information regarding apoptosis).

Other antiproliferative mechanisms of action have been proposed for gallium, including inhibition of protein tyrosine phosphatases and DNA polymerases, but these mechanisms have not been further substantiated.

The natural targeting of gallium to multiplying cancer cells, as is observed in gallium scans, contributes greatly to the efficacy and low toxicity of therapeutically administered gallium. Most healthy cells, even those that are rapidly proliferating, generally do not take up significant amounts of gallium. The inability of Ga to enter heme likely accounts for its lack of accumulation in healthy proliferating hematopoietic cells of the bone marrow. The reasons for the low Ga-avidity of other proliferating healthy cells, such as gastrointestinal mucosal cells and the transient cells of hair follicles, are not known, but may be due to efficient local iron recycling.

Clinical experience: Gallium nitrate became the first preferred gallium compound for experimental and therapeutic use in the USA, due to its relative ease of synthesis and handling. Because aqueous solutions of gallium nitrate are acidic and tend to precipitate gallium hydroxides over time, citrate was added to the solutions; the citrate chelated the gallium, thus neutralizing the pH and promoting stability. The US National Cancer Institute sponsored animal toxicology studies with gallium nitrate, and clinical studies in cancer patients were launched in about 1974 (Adamson et al. 1975).

Small clinical trials found that intravenously administered citrated gallium nitrate (CGN) is effective in non-Hodgkin's lymphoma (43% response) and bladder carcinoma (40% response), with lower response levels in urothelial carcinoma, cervical carcinoma, ovarian carcinoma, squamous cell carcinoma, and metastatic prostate carcinoma (Bernstein 2005). Intravenous CGN must be administered as a slow infusion over several days to avoid renal toxicity. Typical anticancer doses for CGN are 200–500 mg/m^2/day for $\geq$5 days.

CGN administered at 30 mg/m^2/day during alternate 2-week periods, combined with a bimonthly 5-day infusion at 100 mg/m^2/day, together with the M-2 chemotherapy protocol, was highly effective in a study of 13 patients with advanced multiple myeloma. These patients had significantly reduced pain, increased total body calcium, stable bone density, and reduction in vertebral fractures relative to a matched group of 167 patients who received only the M-2 protocol. Most significantly, there was a marked increase in survival in the CGN group (mean survival of 87+ months with several long-term survivors) versus the M-2 only group (mean survival of 48 months with no long-term survivors).

To avoid the inconvenience and renal toxicity of intravenous CGN, gallium maltolate was developed as an orally active gallium compound. Phase I clinical trials have found no renal toxicity or other serious or dose-limiting toxicity (Bernstein et al. 2000). The lack of

renal toxicity is due to the differences in blood speciation between parenterally administered CGN and orally administered gallium maltolate. When CGN is introduced into the blood, much of the gallium forms [$Ga(OH)_4$]$^-$ (gallate) in serum. As a small anionic group, gallate is rapidly concentrated and excreted by the kidney, where it can reach toxically high levels, sometimes forming gallium-calcium-phosphate precipitates in the renal tubules. Gallium from orally administered gallium maltolate, however, becomes almost entirely TF-bound in the blood, with very low renal excretion and no renal toxicity. Anecdotal cases have shown responses to gallium maltolate in advanced hepatocellular carcinoma (Bernstein et al. 2011), lymphoma, metastatic breast cancer, metastatic prostate cancer, and metastatic colorectal cancer.

Gallium 8-quinolinolate is also being developed as an orally active form of gallium. Animal testing has shown activity against some cancers as well as anti-bone-resorptive activity. Phase I clinical trials to date have demonstrated safety and apparent responses in renal cell carcinoma.

Antimicrobial Activity of Gallium

The first biological activity observed for gallium was against pathogenic microbes. In 1931, Levaditi et al. reported that a single dose of gallium tartrate, at 30–45 mg Ga/kg intramuscularly or 15 mg Ga/kg intravenously, eliminated experimental syphilis in rabbits. They also reported that this compound eliminated *Trypanosoma evansi* infection in mice at 225 mg/kg (750 mg/kg was tolerated). Despite these encouraging results, no further antimicrobial studies on gallium were published for several decades.

Emery (1971) found that Ga^{3+} could bind to the fungal siderophore ferrichrome and then be transported into the organism. Subsequently, it was found that other microbial siderophores (low molecular weight Fe^{3+} transporters), including pyoverdine (from *P. aeruginosa*) and deferoxamine, could also bind Ga^{3+}. Suggestions arose for the possible use of Ga^{3+}-substituted siderophores as antimicrobials, but little progress was apparently made in this direction until the late 2000s.

As seen in Table 2, there has been increased research on gallium's antimicrobial properties since the late 1990s, with a number of gallium compounds showing antimicrobial activity at levels that are therapeutically promising. Stojiljkovic et al. (1999) described Ga porphyrins that exploit the heme uptake systems of some bacteria, resulting in highly potent activity against them. Olakanmi et al. (2000) reported that gallium nitrate and gallium transferrin were effective against *Mycobacterium tuberculosis* and *Mycobacterium avium complex*, including those organisms living within human macrophages. Orally administered gallium maltolate at 3–30 mg/kg/day was then found to significantly reduce the number of colony forming units and liver tubercles in guinea pigs infected with *M. tuberculosis* (L.S. Schlesinger 2003, unpublished data).

Gallium appears to be particularly effective against *P. aeruginosa*. This Gram-negative, aerobic bacterium is ubiquitous and highly adaptable, living in soils, plants, and animals throughout a wide variety of environments. It is an opportunistic infector of humans, colonizing open wounds and burns, as well the bladder and lungs. In the presence of sufficient iron, it can form biofilms (commonly in conjunction with other bacterial species) that are highly resistant to immunological attack and to antibiotics. Such biofilms are particularly dangerous when they form in the lungs, as commonly occurs in patients with cystic fibrosis or AIDS. Gallium nitrate was found to inhibit the growth and kill the planktonic form of *P. aeruginosa* dose-dependently at concentrations greater than 1 μM; at 0.5 μM biofilm growth was prevented, and at 100 μM established biofilms were destroyed (Kaneko et al. 2007). In addition, gallium nitrate was effective in treating two murine models of *P. aeruginosa* lung infection. Expression of the transcriptional regulator pvdS, which regulates the synthesis of pyoverdine and other proteins related to iron transport, was suppressed by Ga, contributing to its antibacterial effect (Kaneko et al. 2007).

Gallium maltolate locally administered by subcutaneous injection at 25 mg/kg to burned mouse skin infected with *P. aeruginosa* resulted in 100% survival, versus 0% survival in untreated mice and those treated with an equivalent dose of gallium nitrate (DeLeon et al. 2009). Treatment with gallium maltolate also prevented systemic spread of the bacteria from already colonized wounds. The higher efficacy of gallium maltolate relative to gallium nitrate may be due to its higher lipophilicity (octanol partition coefficient of 0.4), resulting in higher penetration of

Gallium, Therapeutic Effects, Table 2 Antimicrobial activity of gallium compounds

Microorganism	Gallium compound	Activity	References
Bacteria			
Acinetobacter baumannii	Ga maltolate	Local administration inhibited growth in burned mouse skin	DeLeon et al. (2009)
Bacillus cereus	Ga-MTAH[a]	ZOI: 100 μg/mL: 0 mm; 800 μg/mL: 24 mm	Abu-Dari and Mahasneh (1993)
B. subtilis	Diphenyl Ga chloride	MIC: 12.5 μg/mL	Srivastava et al. (1973)
	Ga protoporphyrin IX	MIC: 0.2 μg/mL	Stojiljkovic et al. (1999)
Burkholderia cepacia complex	Ga nitrate	MIC: 64 μg/mL (250 μM Ga)	Peeters et al. (2008)
Citrobacter freundii	Ga protoporphyrin IX	MIC: 1–2 μg/mL (growth medium Fe-restricted w/dipyridyl)	Stojiljkovic et al. (1999)
Escherichia coli	Diphenyl Ga chloride	MIC: >100 μg/mL	Srivastava et al. (1973)
	Ga_2O_3-doped PO_4 glass	Significant activity in disk diffusion assay	Valappil et al. (2008)
	Ga protoporphyrin IX	MIC: <0.5 μg/mL (growth medium Fe-restricted w/dipyridyl)	Stojiljkovic et al. (1999)
	Ga-MTAH[a]	ZOI: 100 μg/mL: 8 mm; 800 μg/mL: 42 mm	Abu-Dari and Mahasneh (1993)
Francisella novicida	Ga lactoferrin	IC50: 1 μM; protected against *F. novicida* nasally introduced to mice	Olakanmi et al. (2010)
	Ga transferrin	IC50: 10 μM	Olakanmi et al. (2010)
F. tularensis	Ga lactoferrin	IC50: 3 μM	Olakanmi et al. (2010)
	Ga transferrin	IC50: 3 μM	Olakanmi et al. (2010)
Haemophilus ducreyi	Ga protoporphyrin IX	MGIC: 32 μg/mL	Bozja et al. (2004)
Helicobacter pylori	Ga protoporphyrin IX	MIC: 0.19 μg/mL	Stojiljkovic et al. (1999)
Klebsiella pneumoniae	Ga protoporphyrin IX	MIC: 2 μg/mL	Stojiljkovic et al. (1999)
Listeria monocytogenes	Ga protoporphyrin IX	MIC: 0.2 μg/mL	Stojiljkovic et al. (1999)
Mycobacterium smegmatis	Ga protoporphyrin IX	MIC: 0.4 μg/mL	Stojiljkovic et al. (1999)
M. tuberculosis	Ga nitrate	IC50: 25–100 μM for bacteria within human macrophages	Olakanmi et al. (2000)
	Ga transferrin	Inhibited iron uptake by the bacteria	Olakanmi et al. (2000)
	Ga maltolate	Orally administered drug showed efficacy in infected guinea pigs at 3.3–30 mg/kg/day	Schlesinger et al. (2003), unpublished data
M. bovis	Ga protoporphyrin IX	MIC: 0.4 μg/mL	Stojiljkovic et al. (1999)
Neisseria gonorrhoeae	Ga protoporphyrin IX	MIC: 0.2 μg/mL	Stojiljkovic et al. (1999); Bozja et al. (2004)
		MGIC: 8 μg/mL; effective in murine vaginal model	
N. meningitidis	Ga protoporphyrin IX	MIC: 0.2 μg/mL	Stojiljkovic et al. (1999)
Proteus mirabilis	Ga protoporphyrin IX	MIC: 2 μg/mL (growth medium Fe-restricted w/dipyridyl)	Stojiljkovic et al. (1999)
Pseudomonas aeruginosa	Ga nitrate	MIC: 2 μg/mL; effective against biofilms; effective in mouse lung infection	Kaneko et al. (2007)
	Ga chloride	Planktonic phase MIC: 2 μg/mL (32 μM)	Banin et al. (2008)
		0.07 μg/mL (1 μM) prevented biofilm formation	
	Ga maltolate	Oral drug showed dose-dependant efficacy against mouse urinary tract infection	Wirtz et al. (2006)
		Local administration was highly effective in mouse burn/infection model	DeLeon et al. (2009)

(*continued*)

Gallium, Therapeutic Effects, Table 2 (continued)

Microorganism	Gallium compound	Activity	References
	Ga-deferoxamine	Planktonic phase MIC: 2 μg/mL (32 μM)	Banin et al. (2008)
		1 μM (0.07 μg/mL) prevented biofilm formation	
		Active together with gentamicin in rabbit corneal infection	
	Ga_2O_3-doped PO_4 glass	Significant activity in disk diffusion assay	Valappil et al. (2008)
	Liposomal $Ga(NO_3)_3$ and gentamicin	Formulations with 0.16 or 0.3 μM Ga more potent than either gentamicin or $Ga(NO_3)_3$ alone against drug-resistant biofilms	Halwani et al. (2008)
P. fluorescens	Ga citrate	Growth lag of 40 h at 1 mM in PO_4-rich medium [note: PO_4 may remove Ga from solution as insoluble Ga phosphate]	Al-Aoukaty et al. (1992)
Rhodococcus equi	Ga nitrate	Growth inhibition observed at 50 μM Ga	Harrington et al. (2006)
	Ga maltolate	MIC: 0.6 μg/mL (8 μM Ga)	Coleman et al. (2010)
Salmonella typhimurium	Ga-MTAH[a]	ZOI: 100 μg/mL: 0 mm; 800 μg/mL: 18 mm	Abu-Dari and Mahasneh (1993)
Staphylococcus aureus	Diphenyl Ga chloride	MIC: 12.5 μg/mL	Srivastava et al. (1973)
	Ga_2O_3-doped PO_4 glass	Significant activity in disk diffusion assay	Valappil et al. (2008)
	Ga protoporphyrin IX	MIC: 1–2.5 μg/mL	Stojiljkovic et al. (1999)
	Ga maltolate	MIC: 375–2,000 μg/mL (0.84–4.5 mM Ga); active against biofilms	Baldoni et al. (2010)
	Ga-MTAH[a]	ZOI: 100 μg/mL: 4 mm; 800 μg/mL: 32 mm	Abu-Dari and Mahasneh (1993)
S. epidermidis	Ga maltolate	MIC: 94–200 μg/mL (210–450 μM Ga)	Baldoni et al. (2010)
Streptococcus pyogenes	Ga protoporphyrin IX	MIC: >4 μg/mL	Stojiljkovic et al. (1999)
Treponema pallidum	Ga tartrate	Eliminated experimental syphilis in rabbits at single dose of 30–45 mg Ga/kg intramuscularly or 15 mg Ga/kg intravenously	Levaditi et al. (1931)
Yersinia enterocolitica	Ga protoporphyrin IX	MIC: 0.4 μg/mL (growth medium Fe-restricted w/dipyridyl)	Stojiljkovic et al. (1999)
Y. pseudotuberculosis	Ga protoporphyrin IX	MIC: 0.2–0.4 μg/mL	Stojiljkovic et al. (1999)
Fungi			
Aspergillus parasiticus	Ga-MTAH[a]	ZOI: 100 μg/mL: 0 mm; 800 μg/mL: 16 mm	Abu-Dari and Mahasneh (1993)
Candida albicans	Diphenyl Ga chloride	MIC: 25 μg/mL	Srivastava et al. (1973)
C. tropicalis	Ga-MTAH[a]	ZOI: 100 μg/mL: 8 mm; 800 μg/mL: 24 mm	Abu-Dari and Mahasneh (1993)
C. neoformans	Diphenyl Ga chloride	MIC: 25 μg/mL	Srivastava et al. (1973)
Fusarium moniliforme	Ga-MTAH[a]	ZOI: 100 μg/mL: 4 mm; 800 μg/mL: 20 mm	Abu-Dari and Mahasneh (1993)
F. solami	Ga-MTAH[a]	ZOI: 100 μg/mL: 8 mm; 800 μg/mL: 34 mm	Abu-Dari and Mahasneh (1993)
Protozoa			
Plasmodium falciparum	$[Ga\text{-}3\text{-}Madd]^{+b}$	IC50 (chloroquine sensitive): ≫20 μM	Sharma et al. (1997)
		IC50 (chloroquine resistant): 0.5-0.6 μM	
	$[Ga\text{-}5\text{-}Madd]^{+c}$	IC50 (chloroquine sensitive): 2 μM	Ocheskey et al. (2003)
		IC50 (chloroquine resistant): ≫15 μM	
	$[Ga\text{-}3\text{-}Eadd]^{+d}$	IC50 (chloroquine sensitive): 0.086 μM	Harpstrite et al. (2003)
		IC50 (chloroquine resistant): 0.8 μM	

(*continued*)

Gallium, Therapeutic Effects, Table 2 (continued)

Microorganism	Gallium compound	Activity	References
	[Ga-3-M-5-Quadd]$^{+e}$	IC50 (chloroquine sensitive): 0.6 μM	Ocheskey et al. (2005)
		IC50 (chloroquine resistant): 1.4 μM	
	Ga protoporphyrin IX	IC50: 127 μM	Begum et al. (2003)
	Ga maltolate	IC50 (chloroquine sensitive or resistant): 15 μM	Goldberg et al. (1998), unpublished data
	Ga nitrate	IC50 (chloroquine sensitive or resistant): 90 μM	
	α-dimethylamino-cyclohexoxyl-dimethyl-Ga	Single dose of 1–3 mg/kg to mice rapidly killed both sexual and asexual forms of the parasite in blood	Yan et al. (1991)
Trypanosoma evansi	Ga tartrate	Eliminated infection in mice at 225 mg/kg	Levaditi et al. (1931)
Viruses			
Human immunodeficiency virus (*HIV*)	*trans*-dichlorotetrakis (benzimidazole) gallium(III) chloride	IC50: 5 μM	Kratz et al. (1992)
	Ga nitrate	IC50: 7 μM	Stapleton et al. (1999)

Abbreviations: *IC50* half maximal inhibitory concentration, *MGIC* minimal growth inhibitory concentration, *MIC* minimal inhibitory concentration, *ZOI* zone of inhibition

[a]Tris(*N*-methylthioacetohydroxamato)gallium(III)

[b][{1,12-bis(2-hydroxy-3-methoxybenzyl)-1,5,8,12-tetraazadodecane}gallium(III)]$^+$

[c][{1,12-bis(2-hydroxy-5-methoxybenzyl)-1,5,8,12-tetraazadodecane}gallium(III)]$^+$

[d][{1,12-bis(2-hydroxy-3-ethyl-benzyl)-1,5,8,12-tetraazadodecane}gallium(III)] $^+$

[e][{1,12-bis(2-hydroxy-3-methoxy-5-(quinolin-3-yl)-benzyl)-1,5,8,12-tetraazadodecane}-gallium(III)]$^+$

tissues and bacteria. Gallium maltolate was also effective when administered orally in a murine urinary tract infection model using *P. aeruginosa* (Wirtz et al. 2006). Several other Ga compounds and formulations have also shown activity against *P. aeruginosa* and biofilm formation (Table 2).

A number of Ga compounds have shown in vitro efficacy against *Plasmodium falciparum* (the major causative agent of malaria), including chloroquine-resistant strains (see Table 2), but no in vivo studies have been published.

Due to its inhibition of ribonucleotide reductase, gallium may have antiviral activity. Stapleton et al. (1999) and Kratz et al. (1992) reported in vitro activity of Ga compounds against human immunodeficiency virus (HIV). Because HIV is a retrovirus that is dependent upon host ribonucleotide reductase to synthesize DNA, a strategy that targets host ribonucleotide reductase may avoid the development of drug resistance.

Gallium compounds have also shown promise against other pathogenic organisms, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Francisella* sp., *Acinetobacter baumannii*, and *Rhodococcus equi* (Table 2). Due to its novel mechanism of action, low toxicity, and activity against drug-resistant strains, there is justification for further exploration of gallium as a potential antimicrobial. Some gallium compounds may be particularly effective when topically applied to the skin, eyes, lungs (by inhalation), bladder (by instillation), or elsewhere, where they can rapidly achieve high local concentrations and can prevent or treat biofilms. Gallium compounds may also be useful as antimicrobial coatings on medical devices.

Anti-inflammatory and Immunomodulating Activity of Gallium

Immunomodulating activity for gallium was noted at about the same time as the early anticancer studies were getting underway, in the early 1970s. Since then, a number of in vitro and animal studies have shown that gallium can act to suppress inflammation and some pathological immunological responses without being generally immunosuppressive.

Gallium appears particularly effective at inhibiting abnormal T-cell-mediated immunological reactions. Ga-TF greatly suppresses alloantigen-induced proliferation of mixed lymphocytes, also reducing the

amounts of IL-2 receptor and increasing the amount of TF-receptor on activated T-cells. It does not, however, inhibit IL-2 secretion or the induction of IL-2-stimulated cytokine-activated killer T-cell activity. Gallium nitrate inhibited both antigen-specific and mitogenic proliferative responses in purified-protein-derivative-specific rat T-cells. While gallium nitrate was found to suppress T-cell activation and some interferon-gamma (IFN-γ) secretion in cell cultures, it did not directly interfere with the normal growth and repair response of gonadal vein endothelial cells to IFN-γ and TNF-α (which may have been enhanced by Ga) (Bernstein 1998).

Intravenously administered gallium nitrate, generally at doses of 10–45 mg Ga/kg/day, has shown efficacy in a number of animal models of T-cell-mediated autoimmune disease. Efficacy has been observed in adjuvant-induced arthritis in rats (reduced synovitis, pannus, subchondral resorption, cartilage degeneration, and periosteal new bone formation), experimental autoimmune encephalomyelitis in rats (a model for demyelinating diseases such as multiple sclerosis, caused by exposure to myelin basic protein (MBP); the proliferative response to MBP was suppressed in T-cells from animals treated with Ga at certain times); experimental autoimmune uveitis in rats (retinal and choroidal inflammation prevented; lymphocyte proliferative responses and humoral immune response decreased); and mouse models of systemic lupus erythematosus and Type 1 diabetes. Some activity in mouse models of asthma and endotoxic shock has also been seen (Bernstein 1998).

Orally administered gallium maltolate showed efficacy in two models of inflammatory arthritis in rats: adjuvant-induced arthritis and streptococcus cell wall–induced chronic arthritis (Schwendner et al. 2005). In both models, oral gallium maltolate dose-dependently reduced joint inflammation, bone degradation, liver and spleen enlargement, and other measures of inflammation. No toxicity was observed.

Gallium nitrate has demonstrated direct immunological effects on macrophages. The effects include transient inhibition of major histocompatibility complex (MHC) class II by murine macrophages; inhibition of inflammatory cytokine and NO secretion by activated murine macrophage-like RAW 264 cells; and inhibition of NO secretion from activated murine ANA-1 macrophages, without inhibition of TNF-α secretion.

In some strains of mice, gallium nitrate was effective at inhibiting acute allograft rejection and prolonging survival. Chronic rejection, however, was not suppressed.

Many of these immunomodulating effects are again likely related to Ga^{3+} being an irreducible mimic of Fe^{3+}. Pro-inflammatory T-helper type 1 (Th-1) cells are much more sensitive to inactivation by iron deprivation than are anti-inflammatory, pro-antibody Th-2 cells (Thorson et al. 1991). Furthermore, Fe^{3+} chelates tend to be highly pro-inflammatory (as they may be siderophores from pathogens); the irreducibility of Ga^{3+} may help to suppress this reaction. The antiproliferative activity of gallium, in this case on certain lymphocytes, may also contribute to gallium's immunomodulating activity.

Effects of Gallium on Bone and on Serum Calcium Levels

A period of intense animal and clinical investigations into gallium's biological activities during the late 1940s and early 1950s revealed the tendency of gallium to concentrate in bone, particularly at sites of bone growth, healing, or tumors. Later, during the early clinical trials of CGN in cancer patients, in the 1970s and 1980s, it was observed that serum calcium levels became normalized in many hypercalcemic patients who were treated with CGN. Hypercalcemia (abnormally high serum calcium, which can be life-threatening) occurs fairly commonly in cancer patients, particularly those with breast and lung cancers. Further clinical and animal studies showed that the reduction in serum calcium was due to inhibited bone mineral resorption rather than increased calcium excretion.

The mechanisms for preferred uptake of Ga at sites of bone remodeling remain poorly understood, though it is known that the uptake is at least partially independent of TF and TF-receptor mediation. Animals or humans lacking TF, that have Fe-saturated TF, or that have TF-receptor blocked by an antibody, show skeletal Ga uptake at the same or greater levels than those with normal TF and TF-receptor. Ga^{3+} in aqueous solution is known to adsorb strongly to calcium phosphates, and gallium phosphates are highly insoluble. Limited experimental evidence (Ga and Ca absorption edge spectroscopy of bone from Ga-treated rats) suggests that about half of the Ga incorporated into bone is

in the form of phosphates. The high phosphate concentrations at sites of bone remodeling may cause the precipitation of Ga-phosphates at these sites.

The discovery of gallium's anti-bone-resorptive effect led to numerous preclinical and clinical studies that explored gallium's mechanisms of action as well as its potential in the treatment of cancer-related hypercalcemia and metabolic bone diseases. These diseases included Paget's disease of bone (characterized by abnormally rapid turnover of bone, often accompanied by pain) and osteoporosis. Ga is observed to dose-dependently inhibit the resorption of bone by osteoclasts (bone resorbing cells of macrophage lineage), without being toxic to the osteoclasts at antiresorptive concentrations. This is in contrast to bisphosphonates, whose antiresorptive activity derives in part from their toxicity to osteoclasts. Gallium was found to directly inhibit acid production by vacuolar-class ATPase in osteoclasts. In patients with Paget's disease treated with CGN, Ga was found concentrated almost exclusively in osteoclast nuclei, presenting the possibility for Ga to act on DNA transcription and expression.

Several controlled clinical studies found CGN (administered as a continuous infusion at 200 mg/m^2 for 5 days) to be effective in the treatment of cancer-related hypercalcemia; comparative studies found CGN to be superior to etidronate or calcitonin, and at least as effective as pamidronate. The US Food and Drug Administration approved this drug in 1991 for the treatment of cancer-related hypercalcemia.

Paget's disease has been successfully treated with low doses of CGN (0.25 or 0.5 mg/kg/day administered by subcutaneous injection). The patients had significantly reduced markers of bone turnover, including serum alkaline phosphatase, urinary hydroxyproline, and *N*-telopeptide collagen crosslinks excretion (Chitambar 2010).

Considerable data exist that suggest anabolic (bone mineral increase) activity for gallium. Evidence includes increased observed bone formation and bone calcium content in Ga-treated rats, and elevated serum alkaline phosphatase in Ga-treated postmenopausal women. CGN dose-dependently (from 5 to 100 μM) decreased constitutive and vitamin D3-stimulated osteocalcin (OC) and OC mRNA levels in rat osteogenic sarcoma osteoblast-like 17/2.8 cells and in normal rat osteoblasts (osteocalcin being an inhibitor of bone formation) (Bernstein 1998).

Effects on Pain

In a brief (7-day) clinical trial of gallium in patients with metastatic prostate cancer, a rapid and significant reduction in pain was noted (Scher et al. 1987). Several years later, in a study of multiple myeloma patients, a significant reduction of pain was recorded for those patients who received gallium nitrate plus a standard form of chemotherapy versus those who received chemotherapy alone (Warrell et al. 1993). In both of these cases, the analgesic effect may have been due to the activity of gallium against the cancer, bone resorption, and/or associated inflammation. Neither of these observations regarding pain reduction were discussed or followed up.

Starting in 2006, a topical cream formulation (0.25 or 0.5 wt.% gallium maltolate in 50% water and 50% hydrophilic petrolatum (Aquaphor®)) has been administered cutaneously to a few individuals suffering from various types of pain (Bernstein 2012). The first case was a 100-year-old woman who had severe facial (trigeminal) postherpetic neuralgia for 4 years and who had responded poorly or not at all to a large variety of systemic and locally administered narcotics, anesthetics, analgesics, antiepileptics, antipsychotics, and other medications. Topically applied, low-dose gallium maltolate has provided nearly complete pain relief that lasts about 6–8 h; the treatment has been used everyday for more than 5 years. The topical formulation has also been found effective in other individuals against postherpetic neuralgia and against pain and itching due to insect bites and stings, spider bites, infections, allergic reactions, inflammation, and burns. The mechanisms for the anti-pain activity are not known; they may relate to gallium's anti-inflammatory activity, plus possible interference with neuropeptides, most of which are Zn-dependent. It is also likely that Ga is acting on one or more presently unknown pain pathways.

Cross-References

- ▶ Gallium in Bacteria, Metabolic and Medical Implications
- ▶ Gallium Nitrate, Apoptotic Effects
- ▶ Gallium Uptake and Transport by Transferrin

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