GALLIUM MALTOLATE

A NOVEL COMPOUND
WITH A UNIQUE ANTICANCER MECHANISM OF ACTION

Gallium has potent antiproliferative activity against cancer cells due to its ability to locally disrupt iron uptake and utilization. It is highly targeted to cancer tissue within the body, as demonstrated by diagnostic gallium scans. Orally administered gallium maltolate delivers gallium efficiently into the bloodstream, where it becomes bound to transferrin, which facilitates high gallium uptake by cancer cells.

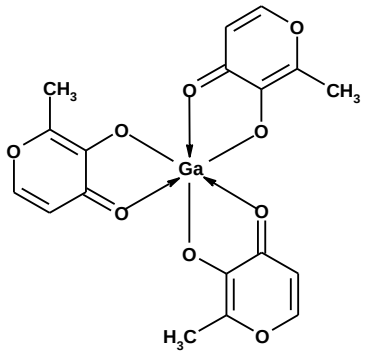
INTRODUCTION

	B	C
	Al	Si
Zn	Ga	Ge
Cd	In	Sn

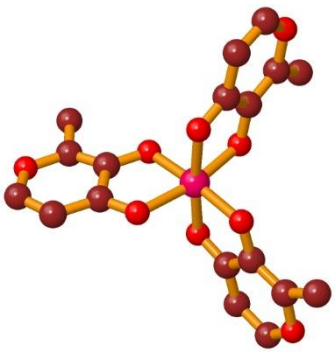
Gallium is well known for its ability to concentrate in cancerous and infected tissues. This ability allows gallium scans (employing ^{67}Ga) to detect a variety of cancers and infections. Recently, antiproliferative mechanisms for gallium have been elucidated. Knowledge of these mechanisms has led to the development of a therapeutic gallium compound—gallium maltolate—that is designed to maximize efficacy and minimize potential adverse effects.

CHEMISTRY

Gallium maltolate, tris(3-hydroxy-2-methyl-4-pyronato)gallium, is a coordination complex consisting of a gallium atom surrounded by three maltolate ligands. Maltol is a naturally occurring compound that is commonly produced during the cooking of foods containing sugars: it is responsible for the aroma of cotton candy and contributes to the fragrance of cookies, cakes, and other baked goods. Maltol is also found in some fruits and is a widely used, FDA-approved food additive. Gallium maltolate is electrically neutral and moderately soluble in both water and lipids. It is stable over a pH range of approximately 5 through 8, a relatively large interval for a metal complex.



Structural formula



Molecular drawing

Gallium Maltolate

MECHANISM OF ACTION

Chemically, gallium behaves remarkably like ferric iron (Fe^{3+}); unlike ferric iron, however, it cannot be reduced to a divalent form under physiologic conditions. Gallium is thus able to compete with ferric iron, which is required for some enzymes to function, but it is not incorporated into hemoglobin or other molecules that contain ferrous iron (Fe^{2+}).

Gallium administered orally as gallium maltolate appears to follow the normal uptake pathway used by iron. Absorption is primarily in the proximal duodenum, where gallium separates from the maltolate ligand and becomes bound to transferrin in the blood plasma. Transferrin, the primary transport protein for iron, has two iron-binding sites per molecule; these binding sites are also able to accommodate gallium ions. Only about a third of the binding sites are typically occupied by iron, so sites are readily available for gallium.

Proliferating cells have a high need for iron: in many cases, iron appears to be the limiting nutrient for cell division. The requirement for iron is due in large part to ferric iron's position at the active site of ribonucleotide reductase (RR), an enzyme essential for DNA synthesis. To acquire iron, many multiplying cells, and particularly cancer cells, express on their surface a large amount of transferrin receptor, which binds to metal-saturated transferrin in the blood. The complex of metal-saturated transferrin and transferrin receptor is taken into the cell by endocytosis; the metal ions are then released, and the transferrin and transferrin receptor are transported out of the cell and recycled. If gallium is present on the transferrin instead of iron, it will compete with intracellular iron and prevent RR from becoming functional. The resulting inability of the cell to synthesize DNA will halt cell division and lead to apoptosis (programmed cell death).

A further anticancer mechanism relates to gallium's ability to strongly inhibit bone resorption. Clinical and preclinical experience with gallium nitrate has demonstrated that gallium blocks the resorptive activity of osteoclasts, without being cytotoxic to these cells. This antiresorptive activity is thought to significantly inhibit metastasis to bone and the destruction of bone by tumors. Animal and *in vitro* data suggest that gallium can, in addition, actually stimulate the regrowth of bone (anabolic activity).

The ability of gallium to selectively target neoplastic tissue, on which it exerts antiproliferative activity by a unique mechanism (competition with ferric iron), together with its ability to potently inhibit bone resorption, make gallium an attractive therapeutic agent.

CLINICAL EXPERIENCE

Intravenous gallium nitrate, approved by the FDA in 1991 for the treatment of cancer-related hypercalcemia, has been administered to over a thousand subjects, mostly cancer patients. Efficacy against several cancers, particularly lymphomas, multiple myeloma, metastatic prostate cancer, and urothelial carcinoma, has been observed. Administration of this compound is, however, limited due to its renal (kidney) toxicity. Intravenous gallium nitrate is eliminated predominately by the kidneys (approximately 49-94% is excreted in the urine in 24 hours) and may transiently reach high concentrations in the renal tubules. In contrast, only about 2% of gallium orally administered as gallium maltolate is eliminated

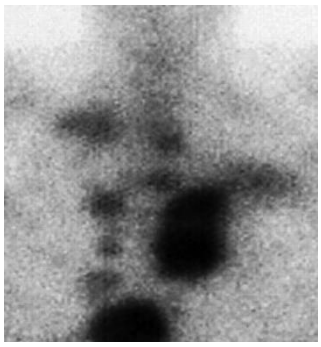
in the urine in 72 hours, and no sign of renal toxicity has been observed for this compound. As mentioned, gallium from oral gallium maltolate is nearly all protein-bound (to transferrin) in the blood plasma, whereas a high proportion of gallium from intravenous gallium nitrate appears to be present as the free gallate ion, $[Ga(OH)_4]^-$. Gallate, being a small charged molecule, is rapidly excreted by the kidneys. It thus appears that oral gallium maltolate, by delivering gallium so that it becomes bound almost entirely to plasma transferrin, should be more efficacious with lower toxicity on a per dosage basis than intravenous gallium nitrate.

Gallium maltolate has been administered to healthy volunteers and to some late-stage cancer patients in Phase I clinical trials. It has been given at doses as high as 3,500 mg/day for 28-day cycles, with no dose-limiting toxicity or serious drug-related adverse effects. The compound has shown high oral bioavailability with an elimination half-life of approximately 17 to 21 hours. Anecdotal efficacy has been observed in patients with lymphoma, end-stage liver cancer (hepatocellular carcinoma), metastatic prostate cancer, metastatic colon cancer, metastatic lung cancer, and metastatic breast cancer.

As an example, a patient with inoperable, late-stage liver cancer, who had not responded to chemotherapy with sorafenib (Nexavar®), was administered a daily dose of oral gallium maltolate. Prior to gallium maltolate treatment, the patient had severe right abdominal pain, elevated serum bilirubin, anorexia, and could not perform most routine activities. A ^{67}Ga scan showed avid gallium uptake by the 20 cm tumor. Within two weeks following the start of gallium maltolate treatment, the patient's right abdominal pain had decreased substantially. Two months following the start of treatment, the patient had resumed most normal activities, serum bilirubin was well within the normal range, and a CT scan showed apparent necrosis and shrinkage of the tumor.

PERSONALIZED MEDICINE

Pharmaceutical therapy is increasingly trending towards the personalized treatment of each patient. This trend is due to the recognition that different individuals, as well as different cases of a particular disease, may respond differently to the same drug. The use of gallium maltolate fits very well into this practice of person-alized medicine. Treatment with gallium maltolate can be targeted to those patients whose cancers are found to preferentially take up gallium in a gallium scan: these are the patients most likely to respond to gallium maltolate therapy.



Gallium scan showing the neck and chest of a patient with Hodgkin's lymphoma. Black regions in the image represent tumors, which had high gallium uptake. The surrounding healthy tissue had very low gallium uptake. [J Nucl Med Tech 28:221-232 (2000)]

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