

Gallium Maltolate: A New Topical Analgesic Agent

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INTRODUCTION

Gallium maltolate, an experimental anticancer compound, has been discovered to have analgesic effects when administered topically to the skin or mucus membranes. In several case studies involving neuropathic pain, topical gallium maltolate demonstrated remarkable efficacy, even when other analgesic agents had been ineffective. The analgesic doses are about a thousandth of the anticancer doses that have been found safe.

Gallium

The semimetallic element gallium has repeatedly shown antiproliferative and anti-inflammatory activities in preclinical and clinical studies [1]. These biological activities stem largely from the chemical similarities between Ga^{3+} and Fe^{3+} (ferric iron), which allow gallium to enter many of the biochemical pathways of ferric iron. Unlike ferric iron, however, gallium is unable to be reduced to the divalent state under physiologic conditions, and it thus cannot participate in redox reactions. These factors make gallium an irreducible, and therefore non-functional, biochemical mimic of ferric iron.

For example, the iron transport protein transferrin can bind to Ga^{3+} , which can then be taken up by rapidly multiplying cells that overexpress transferrin receptor—in particular, many types of cancer cells. Such cells require iron to synthesize DNA, because the enzyme ribonucleotide reductase requires ferric iron in its active site. Gallium, by acting as a non-functional competitive mimic of ferric iron, can act to inhibit DNA synthesis and thus cellular proliferation [1].

The potent anti-inflammatory activity of gallium is due in part to its ability to selectively inhibit the activation and multiplication of T-helper type 1 (pro-inflammatory) cells, and also the secretion of pro-inflammatory cytokines from activated macrophages. Small molecules containing iron tend to be highly pro-inflammatory; it is likely that gallium enters these inflammatory pathways but, due to its lack of redox activity, suppresses inflammation [1].

Gallium Maltolate

Gallium maltolate (GaM) is a coordination complex of gallium and maltol. The hydroxypyrrone maltol is naturally present in many plants and also occurs in baked foods, where it is a sugar degradation product. Due to its octanol:water partition coefficient of 0.41, it is soluble in both aqueous solutions and lipids [2]. This characteristic allows ready penetration of skin and cell membranes, including the membranes of neurons.

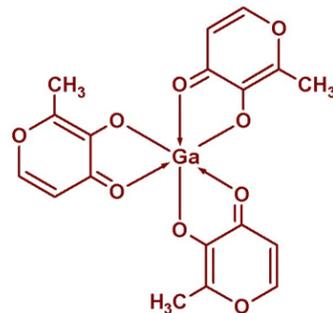
Anti-inflammatory activity has been shown in rat models of rheumatoid arthritis, in which orally administered GaM significantly inhibited ankle swelling, joint inflammation, bone degradation, and enlargement of the spleen and liver [3].

In human cancer clinical trials, GaM has been well tolerated, with no dose-limiting or other serious toxicities observed at oral doses of up to 3500 mg/day for repeated 28-day cycles [2]. In these trials of oral GaM, dramatic pain reduction has often been noted, though it has not been clear if this was strictly an analgesic effect or was primarily related to GaM's anticancer activities.

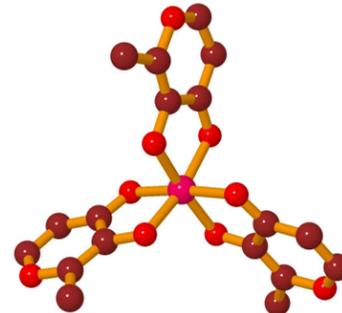
CASE STUDIES

Materials: For most of the case studies reported here, a topical cream formulation was prepared that consisted of 0.5 wt% GaM in an emulsion of 50 wt % water and 50 wt% hydrophilic petrolatum. For one case (tongue cancer), a solution of 1% GaM in water was used.

Dosages: Patients in these cases received a maximum of a few milligrams per day (in many cases, less than one mg/day) of GaM, or about a thousandth of the doses found to cause no serious adverse effects in the clinical trials of oral GaM.



Molecular structure of gallium maltolate



Gallium maltolate molecule from x-ray crystallography

Refractory Postherpetic Neuralgia

A 95-year-old woman developed herpes zoster (shingles) on her face, which was followed by highly refractory postherpetic neuralgia (affecting the mandibular branch of her left trigeminal nerve). For four years, numerous treatments were tried to relieve the severe pain. These treatments included systemic anticonvulsants, tricyclic antidepressants, and opioid analgesics, as well as topical lidocaine and capsaicin, all with unsatisfactory results. The pain was frequently so severe that the patient required hospitalization, and she had become highly depressed.

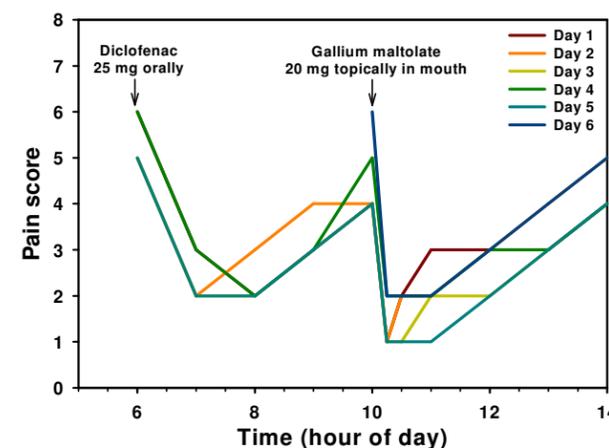
The topical application of gallium maltolate, at a concentration of 0.5% in an emulsion of water and hydrophilic petrolatum, was found to relieve the severe pain in about ten minutes, with the relief lasting for about six to eight hours [4]. The patient used this treatment two to four times per day for more than five years, with no adverse effects and a highly significant improvement in her quality of life. Her severe pain was nearly eliminated by the cream, though mild allodynia sometimes still remained. The patient noted that the GaM cream also rapidly relieved pain from insect bites, spider bites, abrasions, and minor burns. A placebo effect is considered very unlikely in this case, as more than 20 therapies had been tried prior to the use of GaM, most prescribed by her physician and several from alternative medicine sources.

Trigeminal Neuralgia

A 43-year-old woman had a 15-year history of worsening trigeminal neuralgia, affecting the left ophthalmic (V_1) and maxillary (V_2) nerves. She experienced left side pain in the cheek, scalp, ear, upper gums, sinus, nostril, and eye, with severe allodynia, accompanied by left side edema around the jaw and cheek, which interfered with eating and talking. Numerous therapies, including a variety of topical and systemic drugs, as well as chiropractic and acupuncture, produced moderate, temporary relief at most. A topical solution containing 5% ketamine produced moderate relief of allodynia. The patient applied 0.5% GaM in an emulsion base to the left side of her face and forehead. She reported a 50%-75% reduction of pain throughout the affected area within ten minutes, with further pain reduction over the next few hours. After two days of using the GaM emulsion two to three times per day, her facial and jaw edema were nearly eliminated, facilitating eating and speaking. Several weeks after starting to use the GaM emulsion, the patient underwent microvascular decompression surgery for two areas of vascular compression of the left trigeminal nerve. This greatly relieved many of the patient's symptoms; the patient continues to use the GaM emulsion to relieve post-surgical pain as well as remaining neuropathic pain.

Severe Oral Pain Associated With Tongue Cancer

A 32-year-old male physician developed squamous cell carcinoma of the tongue, which metastasized to the face, neck, esophagus, and hyoid bone. An affected portion of the tongue had been surgically resected. The patient experienced severe pain in his mouth due to the effects of the cancer and the surgery. To relieve the pain, the patient received continuous transdermal fentanyl (150 μ g/h) and once-daily oral diclofenac (25 mg). Even with these medications, the patient continued to experience serious pain, at a self-reported level of 4 to 6 on a 10-point scale (where 0 is no pain and 10 is the worst pain imaginable).



For six days, the patient received an aqueous solution/suspension of 1% GaM that he kept in his mouth for a minute or two, and then swallowed. He was asked to record his level of pain, on the 10-point scale just mentioned, at several intervals during the day. As the above graph shows, the GaM consistently produced pain relief of 3 to 5 units every time it was taken. The patient reported that the pain relief from the GaM was preferable to that of his other medications, and produced no side effects.

Refractory Vaginal Pain

A 50-year old developed vaginal inflammation of unknown etiology, accompanied by severe burning pain and erythema. A commercial vaginal ointment product containing 2% of the antifungal agent miconazole (100 mg dose) was used for two days but did not produce pain relief, and inflammation actually increased. Next, a commercial vaginal cream formulation containing 5% benzocaine and 2% resorcinol was tried, but this was also ineffective. Upon vaginal application of the 0.5% GaM cream, pain was relieved within a few minutes, and twice-daily applications of the GaM cream for two days eliminated the inflammation, including all pain and erythema.

Debilitating Neuropathic Foot Pain

A 57-year old, borderline diabetic ($HbA_{1c}=6.5\%$ (48 mmol/mol)) woman presented with chronic bilateral foot pain (on the plantar and dorsal surfaces) and severe allodynia. Her symptoms greatly impeded her daily activities, including walking and her ability to sleep. Following two days of twice daily topical application of 0.5% GaM, the patient was able to walk nearly normally and sleep through the night. Before the GaM treatment, even a light touch to the foot caused unbearable pain; following treatment, touching her foot produced, at most, only occasional slight pain.

Neuropathic Pain Following Hand Injury

A 23-year-old female medical student accidentally cut her left hand at the lateral base below the thumb (see photograph to right). Surgery was performed to close the wound and microsurgically repair nerves, but allodynia remained, with sharp pain shooting up the thumb when the wound was touched.



Topical application of the 0.5% GaM cream was found to nearly eliminate the allodynia. Pain relief lasted 4 to 8 hours, with no side effects.

Other Cases

Two other patients with refractory postherpetic neuralgia (a 73-year-old man and a 72-year-old woman) experienced substantial pain relief from the topical GaM cream. A man with severe, refractory trigeminal neuralgia experienced great pain relief within 20 minutes of applying topical GaM cream. Other individuals have experienced substantial relief of pain and itching following burns, hemorrhoids, insect bites, spider bites, psoriasis, surgery, trauma, and complex regional pain syndrome. The author experienced nearly complete elimination of pain following a bee sting, without numbing.

DISCUSSION

Numerous anecdotal cases indicate that topically administered GaM has analgesic activity, including against neuropathic pain. The mechanisms for this activity are not known, but likely relate in part to gallium's anti-inflammatory activity (as summarized in the Introduction). Gallium may also interfere with the activity of some metalloproteinases and neuropeptides that are implicated in pain generation. These proteins rely on zinc for their activity, and gallium has chemical similarities to zinc as well as to iron [1,5,6]. Further laboratory and clinical studies are warranted to investigate the efficacy and mechanisms of activity of GaM; such research may lead to the discovery of new pain pathways.

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