**INTRODUCTION**

Gallium maltolate, an experimental anticancer compound, has been discovered to have analgesic effects when administered topically to the skin or mucous membranes. In a case study involving chronic neuropathic pain, topical gallium maltolate demonstrated remarkable efficacy, even when other analgesic agents had been ineffective.

**Gallium**

The semimetallic element gallium has repeatedly shown anti-inflammatory and analgesic activities in preclinical and clinical studies [1]. These biological activities stem largely from the chemical similarities between Ga3+ and Fe3+ (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 physiological conditions, and it thus cannot participate in redox reactions as can iron. 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 Ga3+, 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, and 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 hydroxypyrone 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 arthritic 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 [5]. 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**

**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 μg/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 1 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 Posterherpetic 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. The patient has been using 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 is nearly eliminated by the cream, though mild allodynia sometimes still remains. The patient has noted that the GaM cream has 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.

**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.

**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 to gallium’s anti-inflammatory activity, as well as to interference with some metalloproteinases and neuropeptides, which rely on zinc for their activity (since gallium has chemical similarities to zinc, as well as to iron [1,4,5]). 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.

**REFERENCES**


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**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 noticeably eliminate the allodynia, with pain relief lasting 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. Other individuals have experienced substantial relief of pain and itching due to burns, hemorrhoids, insect bites, spider bites, psoriasis, and complex regional pain syndrome. The author experienced nearly complete elimination of pain following a bee sting, without numbing.

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**Gallium Maltolate: A New Topical Analgesic Agent**

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