Gallium Maltolate: A New Topical Analgesic Agent

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INTRODUCTION

Gallium maltolate, an experimental anticancer compound, has been discovered by Bernstein and coworkers to act against neuropathic pain, topical gallium maltolate demonstrated remarkable efficacy, even when other analgesic agents had been ineffective.

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- and Fe-[ferro]-molecular structures, which allow gallium to enter many of the biochemical pathways of ferric ions. Unlike ferric ion, 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 ion.

For example, the iron transport protein transferrin can bind to Ga3+, which can then be taken up by rapidly multiplying cells that overexpress transferrin receptors—in particular, many types of cancer cells. Such cells require iron to synthesize DNA, because the enzyme ribonucleotide reductase requires ferric ion in its active site. Gallium, by acting as a non-functional competitive mimic of ferric ion, 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 of T(H) 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 maltitol. The hydroxyl groups of maltitol are 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 water and organic solvents or oils, which 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 (in 37 patients) [2]. In this patient population, GaM, dramatic pain reduction has often been noted, though it has not been clear if this was due to a chemotherapeutic effect or was primarily related to GaM’s anticancer activities.

CASE STUDIES

Gallium maltolate, a new analgesic agent

Molecular structure of gallium maltolate

Case Study 1: 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 dictotechn (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).

The patient was then treated with 20 mg GaM cream twice daily for 5 days. This resulted in pain relief lasting 6 to 8 hours, with no side effects.

Case Study 2: Refractory Vaginal Pain

A 75-year-old woman with history of cancer of the cervix was referred by her gynecologist for severe analgesic failure, even when using up to 5 mg indomethacin (IM) and ketorolac (IV) daily. The patient had a long history of narcotic and non-narcotic pain, which had been managed with general anesthetics and high-dose IV corticosteroids. She was currently racking weekly injections of morphine and fentanyl, with continuous transdermal fentanyl (20 μg/h) patch, and slowly increasing doses of oral hydromorphone.

The patient was then treated with 20 mg GaM cream twice daily for 5 days. This resulted in pain relief lasting 6 to 8 hours, with no side effects.

REFERENCES


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