Successful Treatment of Refractory Trigeminal Neuralgia with Topical Gallium Maltolate

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INTRODUCTION

Gallium maltolate has produced analgesic and anti-inflammatory activity when administered topically to the skin or mucous membranes. In several previous case studies involving neuropathic pain, topical gallium maltolate demonstrated remarkable efficacy, even when other analgesic agents had been ineffective.

Gallium

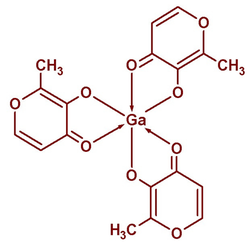
Gallium is a semi-metallic element that has no known essential physiological role, but displays therapeutic biological activities. The element is chemically similar to ferric iron (Fe^{3+}), though unlike Fe, it cannot be reduced to the divalent state under physiologic conditions. This difference is crucial physiologically: it means that, unlike Fe, (1) Ga cannot participate in Fenton-type reactions that produce oxygen free radicals, and so is less toxic than Fe; (2) if Ga competes with or substitutes for Fe in enzymes, the enzymes become non-functional; and (3) Ga does not become incorporated in heme, reducing its toxicity. Ga also shares some chemical similarities with Zn.

Numerous animal studies have demonstrated potent anti-inflammatory activity for gallium, including in models of inflammatory arthritis, lupus, and multiple sclerosis. 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 [1].

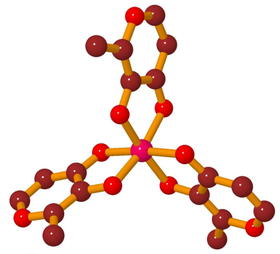
Ga has displayed apparent analgesic activity in human clinical cases of multiple myeloma, metastatic prostate cancer, and hepatocellular carcinoma. We previously reported efficacy of topically applied gallium maltolate (GaM) in cases of postherpetic neuralgia (PHN) and other types of neuropathic pain [2]. The efficacy is hypothesized to be due in part to anti-inflammatory activity, plus possible interference with substance P, certain matrix metalloproteinases, and NMDA receptors [2]. In this pilot study, the aim was to explore the efficacy of topical GaM in the treatment of perhaps the most severe form of neuropathic pain, trigeminal neuralgia (TN).

Gallium Maltolate

Gallium maltolate (GaM) is a coordination complex of gallium and maltol. Maltol is naturally present in many plants; it 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 [3]. This allows ready penetration of skin and cell membranes, including neuronal membranes.



Molecular structure of gallium maltolate



Gallium maltolate molecule from x-ray crystallography

Anti-inflammatory activity of Ga 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 spleen and liver [4].

In human cancer clinical trials, GaM has been well tolerated, with no dose-limiting or other serious toxities observed at oral doses of up to 3500 mg/day for repeated 28-day cycles [3]. In these trials, dramatic pain reduction has often been noted, though it has not been clear if this is strictly an analgesic effect or is primarily related to GaM's anticancer activities.

CLINICAL STUDY

Methods: An open-label pilot study was conducted on a series of 14 TN cases (11 women, 3 men, ages 43-105). Subjects were treated with a formulation consisting of 0.5 wt% GaM in an emulsion of 50 wt% water and 50 wt% hydrophilic petrolatum. The formulation was applied topically 3 times per day to painful regions of the face. In 4 cases, the TN was due to PHN, whereas in the rest it was apparently due to trigeminal nerve compression (usually vascular) or other damage in the pons or nearby areas of the brainstem. The subjects all had experienced TN for between 1 and 20 years, and all had tried numerous medical and surgical therapies with little success. Pain levels were reported over a period of 1 to 3 days on a scale of 0 (no pain) to 10 (worst pain imaginable).

Results: All 14 subjects with refractory TN reported significant pain relief (>3 points) following application of topical GaM (see table). Thirteen of the subjects reported significant pain relief within 20 minutes of topical GaM application, while one subject (M/70) started experiencing significant pain relief after 12 days of daily use. The most extreme case was a 64-year-old woman who had experienced severe postherpetic TN (continuous pain at level 9-10 untreated) for 20 years. Daily morphine plus amitriptyline brought her pain level to 7. Within 20 minutes of first applying topical GaM, her pain level went down to 2 "for the first time in 20 years", and within 2 weeks of daily use she was able to discontinue all use of morphine and amitriptyline. Other subjects reported that they were able to return to work and other activities for the first time in months or years.

Subject Gender/ Age	Indication/ Years with condition	Prior medications	Pain Level (0 to 10 scale)			Years Using Topical GaM
			No medication	Prior medication	Topical GaM	
1. F/64	PTN/21	ami, mor	10	7	0-1	1.25
2. F/105	PTN/10	mor	10	8	2	5.75
3. F/58	TN2/15	oxy, dul, top, pra, gab, nor	10	4-7	1-4	1.50
4. F/44	TN2;TNP/20	tra, bac, ket	7	3	3	2.00
5. M/43	TN1/18	ami, car, gab, top, vlp	10	5	<2	1.00
6. F/46	TN2/2	gab	8	8	1	1.75
7. F/48	TN2/8	hyd, gab, met, ket, nor, oxc	10	6-10	0-4	1.00
8. M/58	TNP/11	gab, hyd, dul	8	5	2	1.50
9. F/85	TN2/8	-	10	-	4	1.00
10. F/52	TN1/14	ami, car, cod	10	5-10	2-7	1.50
11. M/70	TN1/3	gab	9	7	2	0.50
12. F/94	PTN/11	gab, tra	9	8	4	1.00
13. F/92	TN2/5	car	9	7	3	0.50
14. F/72	PTN/1.5	mor, dic	10	4	2	0.75

Indication abbreviations: PTN=postherpetic trigeminal neuralgia; TN1=trigeminal neuralgia type 1 (≥50% episodic pain); TN2=trigeminal neuralgia type 2 (>50% constant pain); TNP = trigeminal neuropathic pain (due to unintentional damage of trigeminal nerve from trauma or surgery)
Drug abbreviations: ami=amitriptyline; bac=baclofen; car=carbamazepine; cod=codeine +acetaminophen; dic=diclofenec; dul=duloxetine; gab=gabapentin; GaM=gallium maltolate; hyd=hydromorphone; ket=topical ketamine; mor=morphine; nor=nortriptyline; oxc=oxcarbazepine; oxy=oxycontin; pra=pramipexole; top=topiramate; tra=tramadol; vlp=sodium valproate

Conclusions

In a series of 14 patients, topically administered gallium maltolate, at a concentration of 0.5%, was effective in relieving refractory trigeminal neuralgia. Pain scores in all cases decreased by about 4-9 points on a 10-point scale. No adverse effects of any kind were reported. These results provide justification for topical GaM entering controlled clinical trials.

REFERENCES

1. Bernstein LR (1998) Mechanisms of therapeutic activity for gallium. Pharmacological Reviews 50:665-682.
2. Bernstein LR (2012) Successful treatment of refractory postherpetic neuralgia with topical gallium maltolate: case study. Pain Medicine 13:915-918.
3. Bernstein LR, Tanner T, Godfrey C, Noll B (2000) Chemistry and pharmacokinetics of gallium maltolate, a compound with high oral gallium bioavailability. Metal Based Drugs 7:33-48.
4. Schwender SW, Allamneni KP, Bendele A, et al. (2005) Efficacy of oral gallium maltolate in acute and chronic models of rheumatoid arthritis (abs.) FASEB Journal 19 (4, Suppl. S, Part 1):A926.

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