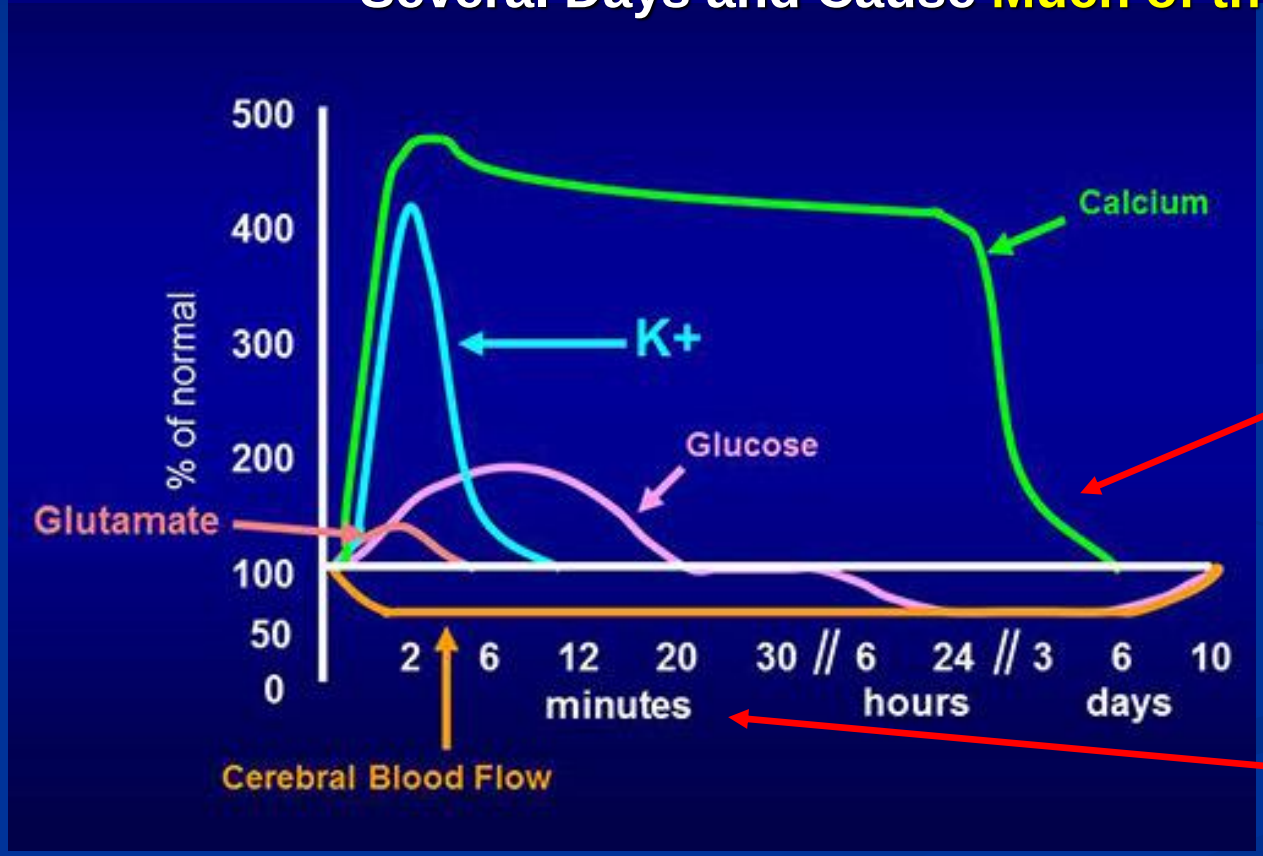
Gallium Compounds
for the
Treatment of Concussion
and
Traumatic Brain Injury

by Jan M. Troup, Ph.D.

The Neurometabolic Cascade Resulting from Concussion

Most Chemical Imbalances from a Concussion are Over in Minutes

These are Not Treatable however Calcium Levels are Increased for Several Days and Cause Much of the Damage

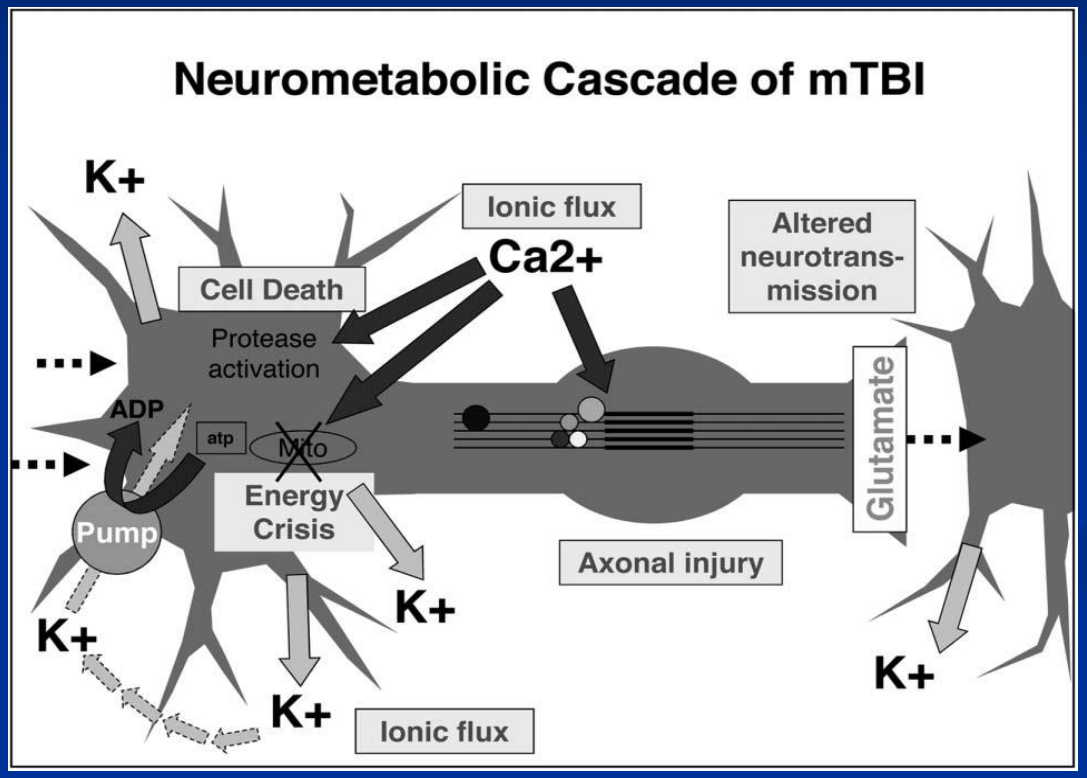


Calcium Levels Increase Immediately 4 - fold and Persist for 2 - 4 days

Potassium, Glutamate and Glucose Imbalances are Elevated Only for Minutes

Christopher C. Giza, David A. Hovda, *Journal of Athletic Training* 2001;36(3):228–235

Ca^{2+} Influx from TBI and Concussion



Christopher C. Giza, David A. Hovda, Neurosurgery 75:S24–S33, 2014

Ca^{2+} Influx through N-type Voltage-Gated Calcium Channels (VGCC's) causes axonal swelling and decreased function

Calcium influx causes Mitochondrial Dysfunction from impaired ATP production giving an Energy Crisis

Potassium Efflux

Glutamate Release

Decreased Glucose Metabolism

National Institute of Neurological Disorders and Stroke (NINDS)

Discussion on Traumatic Brain Injury: Hope through Research, April 15, 2011

"One area of research that shows promise is the study of the role of **calcium ion influx** into the damaged neuron as a cause of cell death and general brain tissue swelling"

ww.ninds.nih.gov/disorders/tbi/detail_tbi.htm.

N-Type Voltage Gated Calcium Channel (VGCC) Blockers

N-type VGCC blockers, SNX-111 (Zirconotide), isolated from Cone Shells and SNX-185 are Neuropathic Pain Blockers and Neuroprotective Agents in Traumatic Brain Injury (TBI)

SNX-111 Found Active for Ischemic Brain Injury in Humans

brain injection is required and treatment has side effects

***J. Cardiovascular Pharmacology*. 1997, Sept., 30(3), 400-403.**

Gallium Nitrate – A Three-Fold Approach to Treat Concussion and TBI

FDA approved Gallium Nitrate is used to reduce hypercalcemia in cancer patients by limiting calcium resorption from bone tissue

Reduction of blood calcium levels after a concussion or TBI should reduce the availability of calcium to neural tissue

Warrell, RP; Brockman, RS; Coonley, CJ; Isaacs, M; Staszewski, H, J. Clinical Investigation, 1984, 73,1487-1490.

Gallium compounds have been shown to be neuropathic pain blockers in animal and human studies

U.S. Patent 8,168,214, Bernstein 2012

Neuropathic pain blockers proceed through the VGCC path believed to be the mechanism for neuron calcium influx

Gallium compounds are known to be powerful non-steroid anti-inflammatory agents for pulmonary and other inflammation

U.S Patent 5,700,487, Gerber et al. 1997

Brain inflammation/swelling is a primary cause of neuron damage

Gallium Compounds for TBI Treatment

$$Ga(NO_3)_3$$

Gallium Nitrate (GN) is a Non-Steroid Small Molecule, Very Soluble in Water and Easily Absorbed Through the Skin.

Gallium Nitrate reduces blood Calcium Levels, reduces Pain and Inflammation and additionally is anti-bacterial, anti-pathogen and a blood clotting agent

Hundreds of gallium compounds exist that have similar physiological properties to gallium nitrate

Gallium Nitrate Dose Levels

Gallium Nitrate (Ganite) dose for **hypercalcemia** in cancer patients is 200 mg/m^2 or approximately **5 - 6 mg/kg** of body weight per day for 5 days.

Studies on humans with doses of **4 - 10 mg/kg** of GN for lymphoma and a variety of other **forms of cancer** over 5 - 7 days have been tested without adverse effects.

Case study for **plantar fasciitis** treatment with a **14% solution of GN**, absorbed through the bottom of the foot for 30 minutes every other day for three days. Treatment eliminated the pain immediately and the inflammation disappeared in a week that had persisted for 6 months. Minor side effects were observed 24 hours after each treatment. Jan M. Troup

50,000 GN doses of **11 mg/kg** of body weight given to **horses for navicular bone inflammation** with no reported evidence of toxicity. George Eby 2004

Gallium Nitrate Treatment for Hypercalcemia in Cancer Patients

TABLE 1
Response of patients with cancer-related hypercalcemia to continuous infusion of gallium nitrate

Patient	Cancer Diagnosis	Total Serum Calcium[1] Pre-Treatment	Total Serum Calcium[1] Post-Treatment	Daily Dose of Gallium Nitrate
				$(mg/m^2) \times$ days
1	Breast	13.6	8.9	200×5
2	Lymphoma	14.0	6.7	200×6
3	Head & Neck	12.3	8.5	200×5
4	Breast	14.4	7.7	200×6
5	Lumphoma	15.6	8.6	200×7
6	Lung	12.5	7.0	200×5
7	Lung	12.7	9.4	200×5

[1] Serum concentration expressed in mg/dl (formal range, 9.0—10.8 mg/dl).

Dose of 200 mg/m^2 for 5 or more days reduced serum calcium levels by 25 – 50%

Patent: Warrell R, Bockman R, The use of gallium salts for the manufacture of pharmaceutical compositions for the treatment of disorders of calcium homeostasis, EP 0109564 B1

Gallium Nitrate (Ganite) Compared to Calcitonin for Serum Calcium Reduction

Change in Corrected Serum Calcium by Time from Initiation of Treatment

Time Period[1] (hours)	Mean Change in Serum Calcium[2] (mg/dL)	
	GANITE	Calcitonin
24	-0.4	-1.6*
48	-0.9	-1.4
72	-1.5	-1.1
96	-2.9*	-1.1
120	-3.3*	-1.3

[1] Time after initiation of therapy in hours.

[2] Change from baseline in serum calcium (corrected for albumin).

* Comparison between treatment groups ($p < 0.01$).

Up to a 2.5 fold greater reduction than calcitonin for calcium regulation

www.ganite.com/hcp/efficacy_studies.shtml

Study of a Moderate Traumatic Brain Injury on Mice Treated with Gallium Nitrate

Study Conducted by Dr. Tanea Reed and Co-workers at Eastern Kentucky University (July 2015)

Test the Oxidative Stress Levels on Mice Given a Moderate Controlled Cortical Contusion and Treated with Gallium Nitrate (GN)

Oxidative Stress is a Reliable Biomarker for Traumatic Brain Injury but Not Yet Known to be Causal

Oxidative Stress, a Biomarker for Traumatic Brain Injury:

Mendes Arent A, de Souuza LF, Allz R, Dafre AL, Perspectives on molecular biomarkers of oxidative stress and antioxidant strategies in traumatic brain injury., BioMed Res Int.,2014;2014:723060.

Study was Directed and Financed by Jan M. Troup, Ph.D.

Moderate Traumatic Brain Injury on Mice Treated with Gallium Nitrate

Study Details:

A. Twenty C57BL/6HNsd mice were used (one succumbed during the injection)
   Four sham mice (craniotomy only, no injury)
   Four saline mice treated 15 minutes post injury
   Four saline mice treated 30 minutes post injury
   Three GN mice treated 15 minutes post injury
   Four GN mice treated 30 minutes post injury

B. Moderate controlled cortical contusion – piece of the skull was removed and replaced after injury

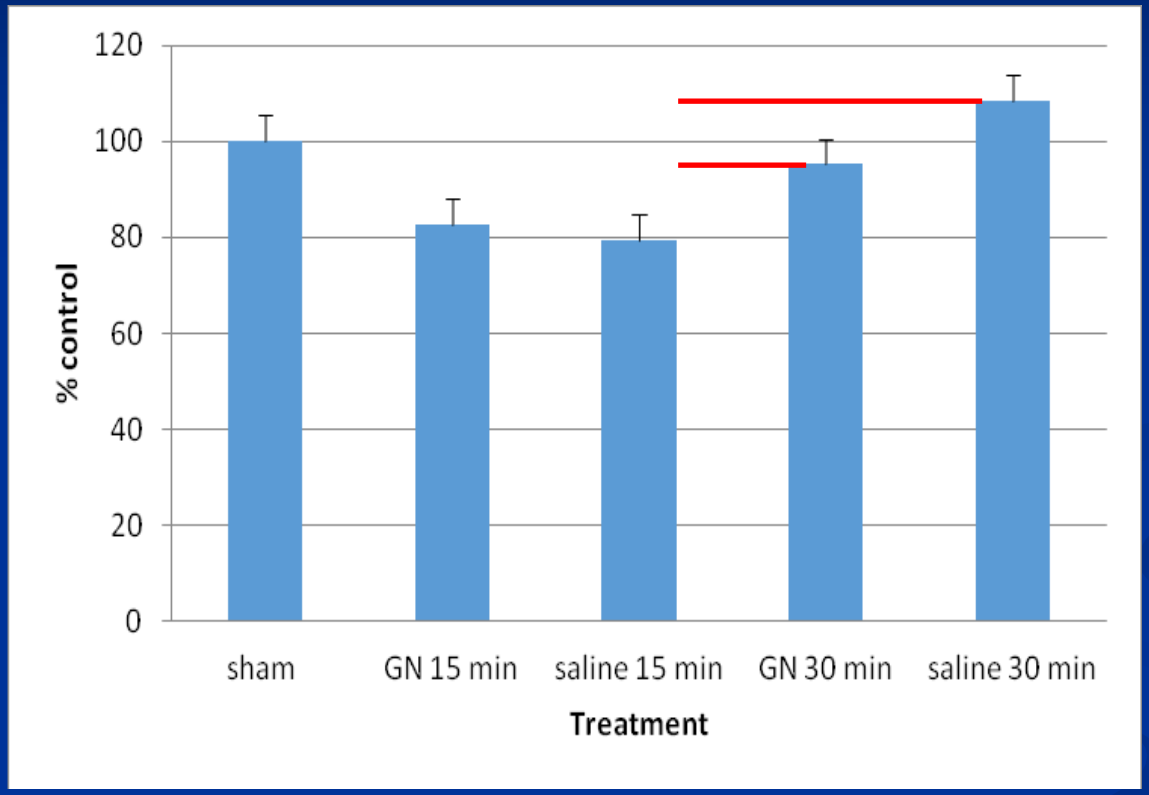
C. Intraperitoneal injection of 10 mg/kg $Ga(NO_3)_3.(H_2O)_9$ or 6 mg/kg $Ga(NO_3)_3$, dose similar to 200 mg/m^2, human dose

D. 24 hours post injury assays were performed on whole brain homogenate

E. Duplicate western blot immuno assays for protein carbonyl oxidation (anti-2,4-DNP) and protein nitration (anti-3-nitrotyrosine)

Moderate Traumatic Brain Injury on Mice Treated with Gallium Nitrate

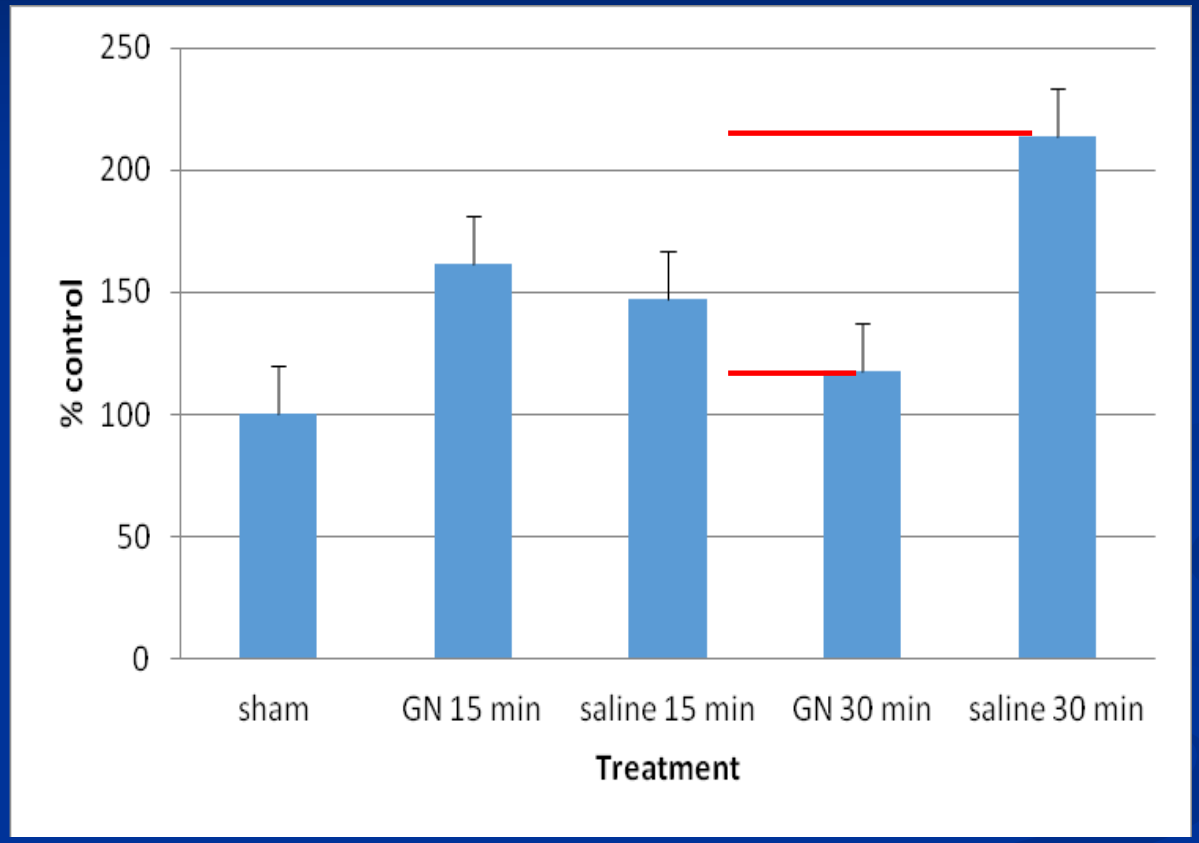
Protein Carbonyl Analysis



GN treated mice at 30 minutes post injury showed a 15% reduction p = 0.1 (90% significance) in Protein Carbonyl Oxidation relative to saline treated mice

Moderate Traumatic Brain Injury on Mice Treated with Gallium Nitrate

Protein Nitration, 3-nitrotyrosine Analysis



GN treated mice at 30 minutes post injury showed a 96% reduction p = 0.01 (99% significance) in Protein Nitration relative to saline treated mice

Results from a Moderate Traumatic Brain Injury on Mice Treated with Gallium Nitrate

A. **Protein Carbonyl Oxidation** and **Nitration** are proven independent markers for Traumatic Brain Injury and Concussion and have been shown to be significantly reduced by Gallium Nitrate therapy.

B. Dose used for mice was similar to the **daily dose of 6 mg/kg used to treat hypercalcemia** in cancer patients.

C. Results are remarkable since gallium nitrate is a **oxidizing agent** but showed reduced neural oxidative stress markers post injury.

(continued)

Results from a Moderate Traumatic Brain Injury on Mice Treated with Gallium Nitrate

D. This was the first attempt of a TBI animal treatment using gallium nitrate.

The injection time of 30 minutes post injury was based on chemical cascade data for TBI but this timing is an unknown variable.

E. Additional work should look at different dose levels, multiple doses given for several days after injury, varying GN injection times after injury and additional assays measured longer than 24 hours post injury.

F. No adverse motor skills or activity levels were observed in the animals during the study.

Treatment Methods using Gallium Nitrate

The chemical cascade resulting from **brain damage occurs rapidly after an injury** and gallium compounds can be administered rapidly by the most convenient method

Gallium treatment should be thought of as a **Time of Injury** or **First Aid** for Traumatic Brain Injury

Oral, Nasal Inhalation, Injection or Transdermal Patch are the preferred methods of treatment for **Sports Related** or **Military Injury** due to ease of application.

Transdermal Patch is particularly attractive since gallium nitrate is rapidly absorbed through the skin and the patch could be applied from a first aid kit while the patient is being evaluated and then removed if found not to be necessary.

Patent for TBI using Gallium Compounds

U.S. Patent 9,205,108 B2 Issued December 8, 2015

for

Treatment of Traumatic Brain Injury by Using Gallium Compounds to Reduce Oxidative Stress Levels

by

Jan M. Troup, Ph.D.

Patent covers treating traumatic brain injury with a therapeutically effective amount of any Gallium Compound administered by any normal method within an effective time period subsequent to the injury

Conclusion:

Gallium Nitrate is a Possible Treatment for Concussion and Traumatic Brain Injury