IV Therapy to Improve Quality of Life in the patient with Cancer

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Outline

I. Concepts in the care of end stage oncology patients

a. Assessment, management and interventions appropriate in palliative care and end of life

b. Uses of targeted nutrient rich hydration solutions in the palliative setting

c. Case discussions regarding use of IV therapy in the fragile or end of life patient setting

Assessment, management and interventions appropriate in palliative care and end of life

Benefits and risks of parenteral nutrition in patients with cancer

Nutritional status can have a significant impact on patients with cancer, and PN may help some patients respond better to treatment.

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TPN versus PPN

- TPN:
  - A solution containing all the required nutrients including protein, fat, calories, vitamins, and minerals, is injected over the course of several hours, into a vein. TPN provides a complete and balanced source of nutrients for patients who cannot consume a normal diet.
- PPN:
  - With peripheral parenteral nutrition (PPN) nutrients are supplied via a peripheral vein, usually a vein in the arm. Another term for PPN is peripheral venous nutrition (PVN)

MALNUTRITION IN ONCOLOGY

- Malnutrition is the most common secondary diagnosis in cancer patients. Even patients who are eating can become malnourished because of specific biochemical and metabolic changes associated with cancer. These metabolic changes impair nutritional status and contribute to cancer-related malnutrition, anorexia, and cachexia. At least 50% of cancer patients are cachetic.3 Recent reviews indicate cachexia is even more widespread among patients with advanced cancer.4

- In the palliative setting, PN can extend survival; however, it is associated with risks such as line infections, fluid and electrolyte imbalances, and liver and pancreatic issues. There are general guidelines suggested for the use of PN in patients with advanced cancer.15 First, standard oral diet or enteral nutrition is always the preferred form of nutrition. PN should only be used in patients with a nonfunctioning GI tract, if death will occur from starvation earlier than it would from disease progression, and the patient has a life expectancy of at least 2 to 3 months. Finally, parenteral nutrition improves quality of life for the patient in the last part of life. PN administration to patients with advanced cancer presents ethical and moral considerations that should be carefully considered when deciding on the care plan for cancer patients in the final stages of life.

3. K Kern KAKA, Norton JAJA. Cancer cachexia. JPEN J Parenter Enteral Nutr. 1988;12(3):286-298.

4. Bozzetti F, Mariani L. Defining and classifying cancer cachexia: a proposal by the SCRINIOWorking Group. *JPEN J Parenter Enteral Nutr*. 2009;33(4):361-367.

15. Mirhosseini M, Faisinger R. Fast facts and concepts #190 Parenteral nutrition in advanced cancers patients. End of Life/Palliative Education Resource Center. http://www.eperc.mcw.edu/FileLibrary/User/jrehm/fastfactpdfs/Concept190.pdf. Accessed July 18, 2011.

Medical Work-up

- Comorbidities
- Concurrent / Prior treatment
- Prior response to IV therapy
- Screening labs

Medical Work-up

- Comorbidities:
  - For IV Tx the most important involve:
    - Cardiovascular
    - Renal
    - Hepatic
    - Immune
- Concurrent / Prior Treatment:
  - Other IV Tx
  - Chemo

Medical Work-up

- Prior response to IV therapy
  - Anxiety
  - Reactions / Allergy
  - Access Issues

Medical Work-up

- Screening labs
  - Minimum:
    - CBC+Diff+PLT
    - CMP / Chem 14 (ALB/T.Prot/BUN/CRE/AlkPhos Glucose/T.Bili/K/Ca/Cl/CO2/Na/ALT/AST)
    - Lipid profile
    - G6PD *(See IV Vitamin C Presentation notes)
  - Any other labs required to follow the patient and comorbidities.

Uses of targeted nutrient rich hydration solutions in the palliative setting

Rehydration

- Rehydration therapy is helpful in many instances and is not uncommon in offices providing IV therapy.

- Issues involved around rehydration therapy are:
  - Level of dehydration
  - Electrolyte imbalances
  - Complications:
    - Speed shock
    - Volume Overload

Rehydration

- Fluid replacement for one day calculated at 1500 to 2000 mL total requirement.

- Acute dehydration due to fever, vomiting, diarrhea… can be safely compensated for over a 4 to 8 hour period.

  - Common nursing orders:
  - 500 to 1000 mL Saline, D5W or Ringers Lactate at 125 to 250 mL/hr acutely X 1 to 2 hours, then slow the rate to not more than 125 mL/hr

Rehydration induced “fluid overload”:

- **Cause:** Infusing an ISOTONIC solution too quickly.
  - Watch the elderly, those with compromised kidney function and or CHF.
- **Signs:** Edema, Hypertension, Pulmonary edema (including dyspnea & crackles)
- **Treatment:**
  - Slow fluid infusion
  - Heat to dilate peripheral circulation
  - O2 administration
  - Diuretics necessary in severe cases

Rehydration:

- Always employs:
  - Isotonic or mildly hypotonic solutions
  - These hydrate the ECF and Cells
- Never employs Hypertonic solutions
  - Hypertonic solutions dehydrate the ECF and cells

Base IV Solutions

- Sodium Chloride Solutions
  - 0.45% HYPOTONIC Half-Normal Saline “1/2 NS”
    - **154 mOsm/L**
    - Can be infused alone as a hydration bag
    - Is the LOWEST osmolarity infused without other additives.
    - Often employed as a base solution for other additives
  - 0.9% ISOTONIC Normal Saline “NS”
    - **308 mOsm/L**
  - Saline Infusions:
    - Good agent for volume stabilization when other electrolytes not required.
    - Good agent in hyponatremia and hypochloremia

Base IV Solutions

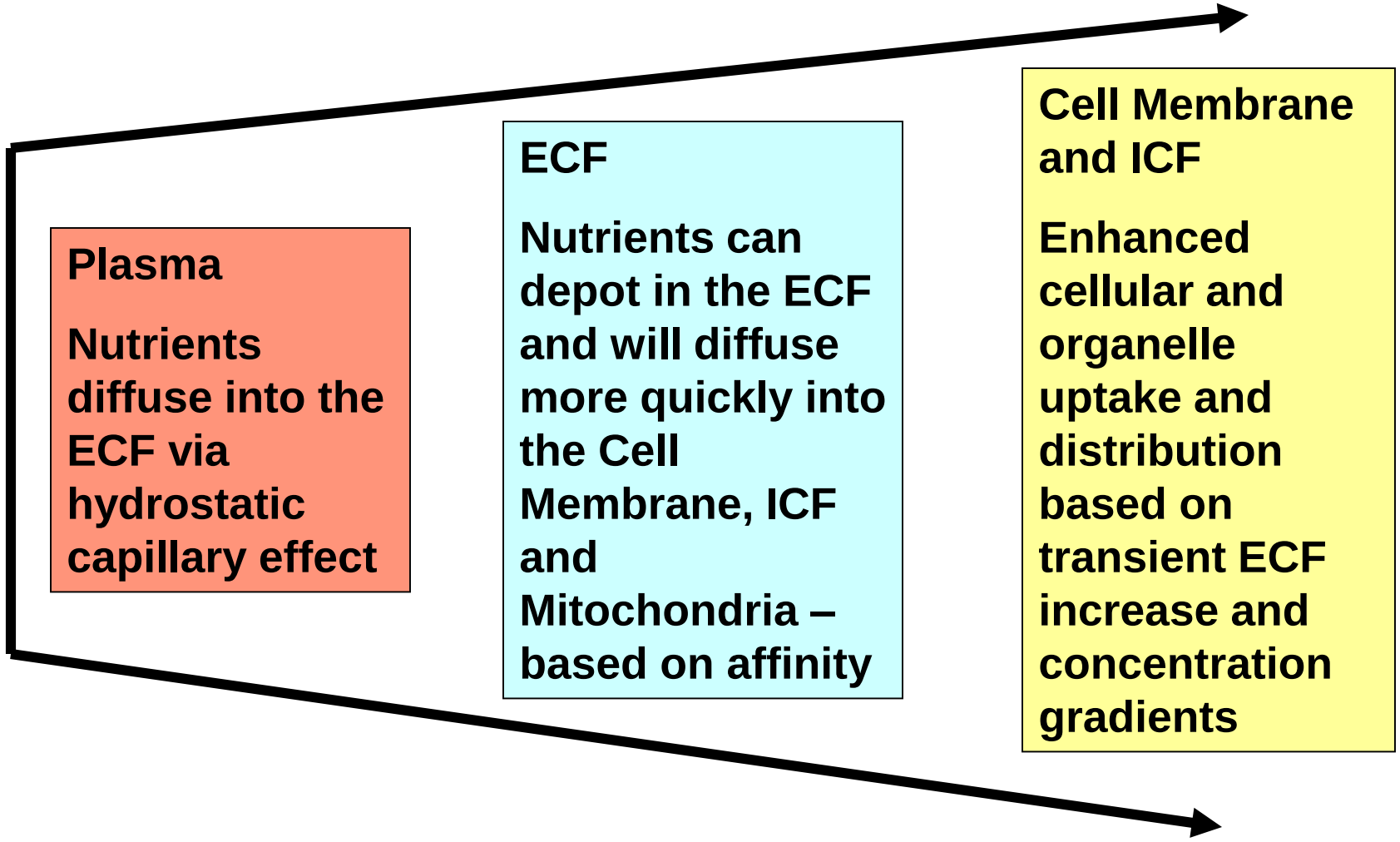
- Sterile Water:
  - NEVER used without additives (-0- osmolarity = hemolysis and death) but is an excellent base for IV Nutrients.

- Ringer's Lactate: "Hartmann's solution".
  - Very similar to the ECF electrolytes.
    - **273 mOsm/L**
  - Helpful in all acidosis (except lactic) as lactate metabolism creates bicarbonate / acid stabilizing metabolites.
  - **Do not use** in Addison's or hepatic disease where lactate metabolism is impaired.

Base IV Solutions

- Dextrose in Water
  - D5W: 5% Dextrose in Water.
    - ISOTONIC (can become hypotonic during infusion if dextrose is metabolized quickly).
    - **260 mOsm/L**
  - 1.5 to 2 liters / day average.
    - Good solution base for many antibiotics.
    - Often employed in patients with labile blood sugar control. (May increase insulin need in IDDM.)
    - RAPID INFUSION CAUSES SEVERE NAUSEA AND VOMITING
      - 125 – 250 mL / Hour is safe, unless patient is volume depleted – then 250 – 500 mL / Hr may be tolerated

Direct effect after infusion; Exclusive of specific channel or transport activity:



Custom Rehydration Solutions with Nutrients

- Examples will be given in the Protocol section on the second day.

Pain

Magnesium and Cancer Pain

- Consider the role of magnesium in cancer related pain as an adjunct to other therapies.

- Our clinical experience shows that when titrated to patient cardiac tolerance higher doses of parenteral magnesium can provide pain relief due to a number of potential mechanisms.

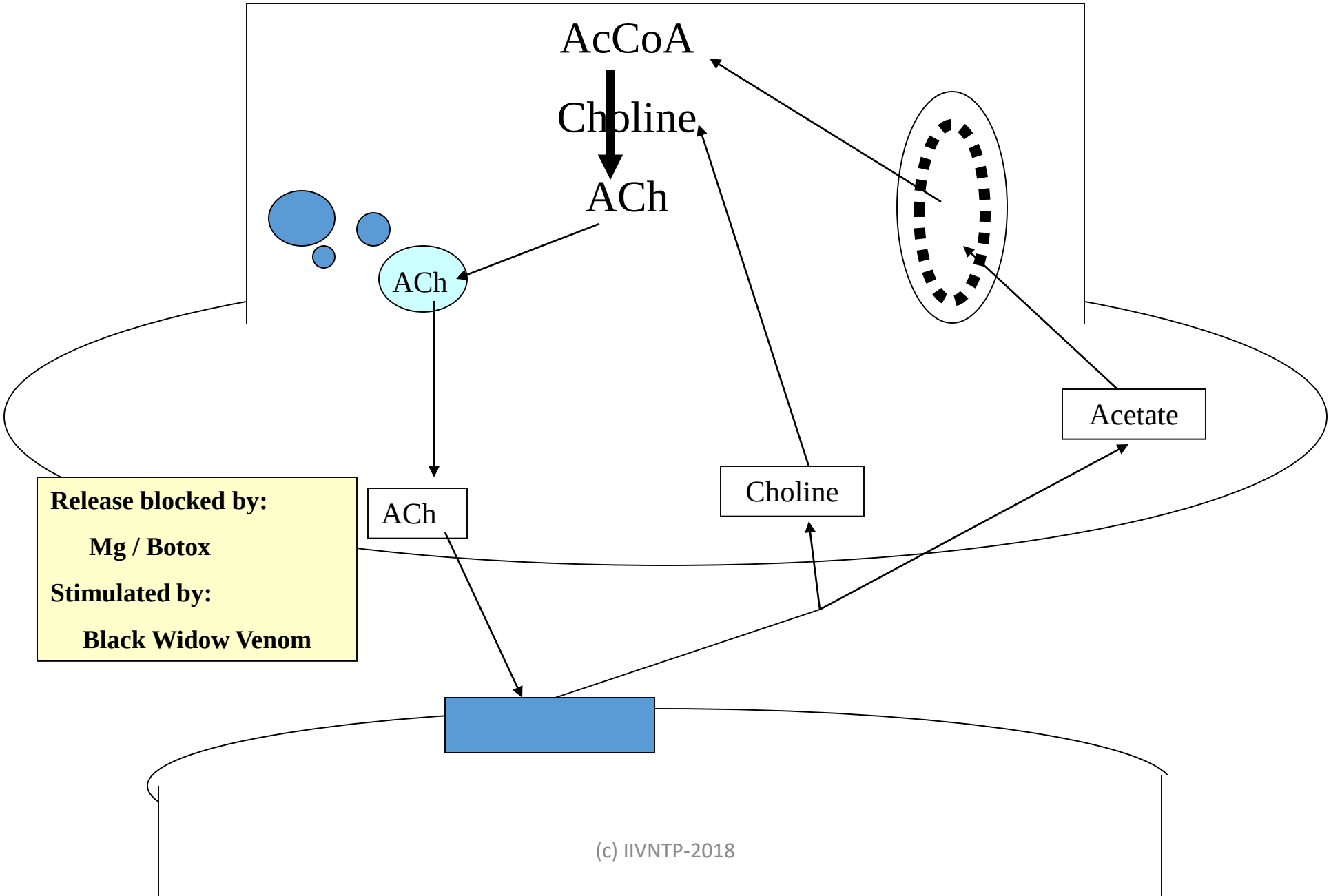
- Dose tolerance is wide and must be titrated, but average magnesium sulfate dosing for pain conditions can be in the range of 2 to 8 (or more) grams in a 500 – 1000 mL IV solution given over 1-4 hours.

Magnesium Effect on Muscle Tissue:

Effect:	Skeletal Muscle	Smooth and Cardiac Muscle
Calcium Channel blockade	+++	+++
NMDA Receptor antagonist: * Via central regulation	+++	+++
Acetylcholine release blockade:	+++	

Additionally can act in the CNS to block Ca++ channels and inhibit central pain issues.

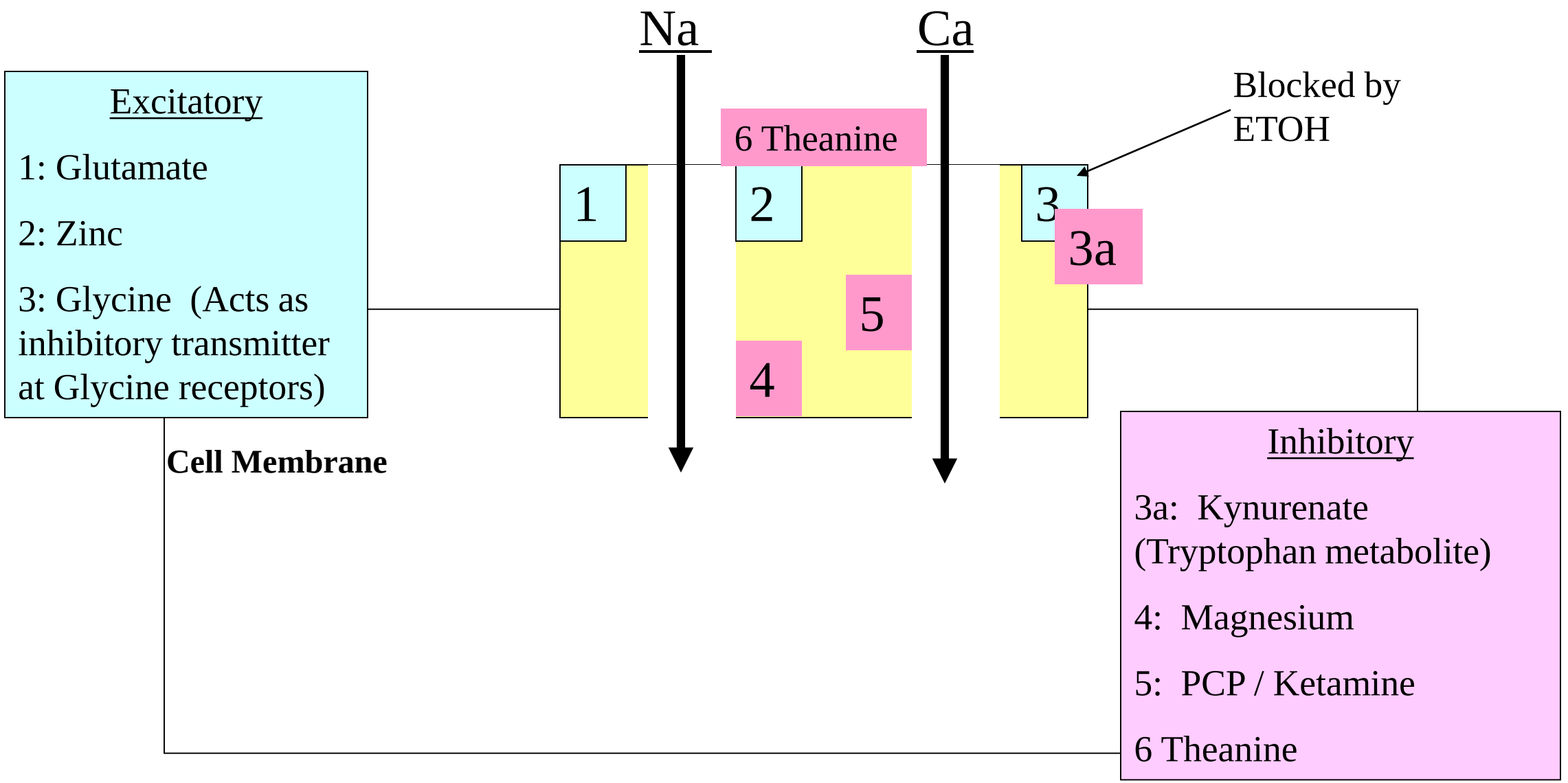
Acetylcholine Synapse



NMDA Receptor - Inhibited by Mg+

- Primary excitatory receptor complex
- Often categorized with other excitatory “Glutamate” class receptors
  - N-methyl-D-aspartate (Na/Ca/K)
  - Kainate (Na/K ?)
  - AMPA (Na/K)
  - AP4 (Presynaptic inhibition)
  - ACPD (IP3 / DAG)

NMDA Receptor



Hypomagnesemia in oncology patients

- Hypomagnesemia Is Prevalent in Patients Undergoing Gynecologic Surgery by a Gynecologic Oncologist
- Ulm, Michael A. MD, MS; Watson, Catherine H. MD; Vaddadi, Prethi MD; Wan, Jim Y. PhD; Santoso, Joseph T. MD
- **Abstract**
- Objective: The aim of this study was to assess the incidence of and risk factors for hypomagnesemia in patients undergoing gynecologic surgery by a gynecologic oncologist.
- Methods: A retrospective chart review was performed on all patients undergoing surgery for gynecologic pathology from July 2011 to July 2015 by a single surgeon. Demographic data, surgical indication, surgery performed, preoperative laboratory values, postoperative laboratory values, and medical history were examined. Hypomagnesemia was defined as less than 1.8 mg/dL. Hypermagnesemia was defined as greater than 2.5 mg/dL.
- Results: Six hundred sixty-nine patients were identified for analysis. One hundred ninety-seven patients had hypomagnesemia (29.4%). Four hundred sixty-six patients had normal magnesium levels (69.5%), and 6 patients had hypermagnesemia (1%). Among patients with benign disease, 24.9% had preoperative hypomagnesemia compared with 32.7% of patients with a gynecologic malignancy. African American race ($P = 0.041$), diabetes mellitus ($P < 0.001$), and malignancy ($P = 0.029$) were all associated with preoperative hypomagnesemia. Diabetes and major surgery were associated with postoperative hypomagnesemia ($P = 0.012$ and $P = 0.048$, respectively). Hypomagnesemia was associated with increased preoperative and postoperative pain ($P = 0.049$ and $P < 0.001$, respectively) as well as postoperative hypokalemia ($P = 0.001$). Age, body mass index, hypertension, cancer type, hematocrit, surgical indication, and length of hospital stay were not associated with hypomagnesemia.
- Conclusions: Perioperative hypomagnesemia is prevalent in patients undergoing gynecologic surgery by a gynecologic oncology, especially in patients who have a gynecologic malignancy. **We recommend routine preoperative and postoperative evaluation of serum magnesium in all patients undergoing gynecologic surgery by a gynecologic oncologist**.
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- International Journal of Gynecological Cancer:September 2016 - Volume 26 - Issue 7 - p 1320–1326, doi: 10.1097/IGC.0000000000000766

Recovery following chemotherapy and radiation therapy:

- Generally patients need:
  - Nutrition
  - Hydration
  - Tissue repair
  - Antioxidant support
  - Nervous system and endocrine support

Neuro-regeneration

- Neurological cells (and all others) are incredibly sensitive to mitochondrial damage, cell membrane damage and other effects.
- Many oncologic therapies have deleterious effects on the cell matrix and nerve function, leading to significant decreases in quality of life.
- Supplementation and augmentation of glutathione function can aid in the regeneration of all damaged neurological tissues.

Glutathione

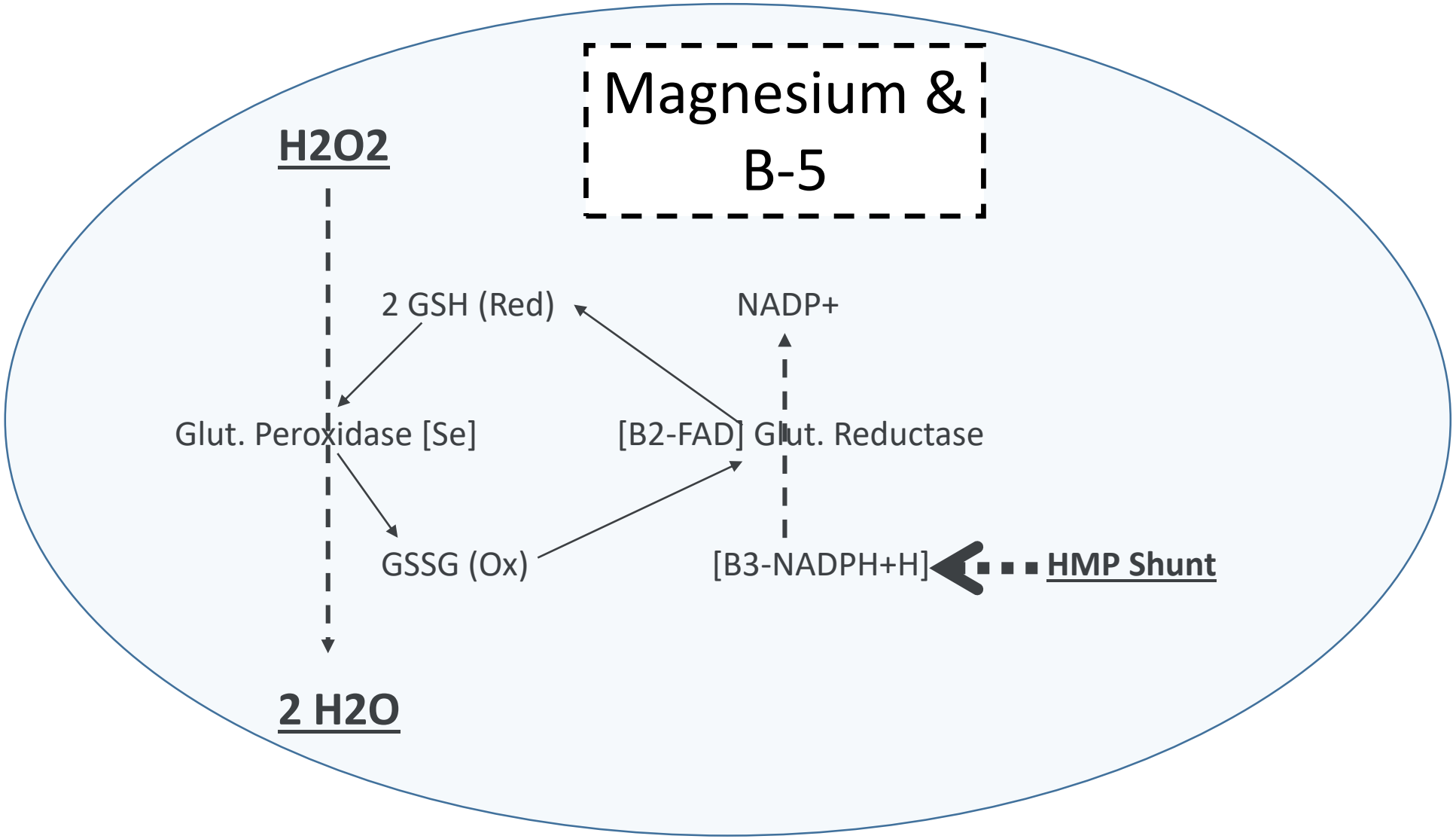
- Proven beneficial in pre loading doses prior to radiation.
- Studies showing further benefit post radiation treatments
- Decreases post treatment neuropathy
- Supports p53 activity through the redox modulation enhancing tumor apoptosis.

Glutathione

- Glutathione (GSH) and the augmentation of its function appear in early trials at the Bastyr Integrative Oncology Research Center to aid greatly in repair of radiation and chemotherapy induced neuropathies.

- Data are preliminary, but if general pharmacokinetic and dynamic parameters are observed GSH can be safely used in the patient with cancer.

Glutathione and Cofactors



Glutathione and B-5

- Slyshenkov VS, Dymkowska D, Wojtczak L. Pantothenic acid and pantothenol increase biosynthesis of glutathione by boosting cell energetics.FEBS Lett. 2004 Jul 2;569(1-3):169-72. Source Nencki Institute of Experimental Biology, Pasteura 3, 02-093 Warsaw, Poland. PMID: 15225628

- Wojtczak L, Slyshenkov VS.Protection by pantothenic acid against apoptosis and cell damage by oxygen free radicals--the role of glutathione. SourceNencki Institute of Experimental Biology, Pasteura 3, 02-093 Warsaw, Poland. LWAC@nencki.gov.pl PMID: 12897429

Glutathione and RBC Mg

***Abstract*—**Recent evidence suggests that the endogenous antioxidant glutathione may play a protective role in cardiovascular disease. To directly investigate the role of glutathione in the regulation of glucose metabolism in hypertension, we studied the acute effects of in vivo infusions of this antioxidant (alone or in combination with insulin) on whole body glucose disposal (WBGD) using euglycemic glucose clamp and the effects on total red blood cell intracellular magnesium (RBC-Mg) in hypertensive (n520) and normotensive (n530) subjects. The relationships among WBGD, circulating reduced/oxidized glutathione (GSH/GSSG) levels, and RBC-Mg in both groups were evaluated. The in vitro effects of glutathione (100 mmol/L) on RBC free cytosolic magnesium (Mgi) were also studied. In vivo infusions of glutathione (15 mg/min3120 minutes) increased RBC-Mg in both normotensives and hypertensives (1.9960.02 to 2.1360.03 mmol/L, *P,0.01, and 1.6960.03 to 1.8160.03 mmol/L, P,0.01, respectively). In vitro GSH* but not GSSG increased Mgi (17963 to 21465 mmol/L, *P,0.01). In basal conditions, RBC-Mg values were related to* GSH/GSSG ratios (*r50.84, P,0.0001), and WBGD was directly, significantly, and independently related to both* GSH/GSSG ratios (*r50.79, P,0.0001) and RBC-Mg (r50.89, P,0.0001). This was also true when hypertensive and* control groups were analyzed separately. On multivariate analysis, basal RBC-Mg (*t56.81, P,0.001), GSH/GSSG* (*t53.67, P,0.02), and blood pressure (t52.89, P,0.05) were each independent determinants of WBGD, with RBC-Mg* explaining 31% of the variability of WBGD. **These data demonstrate a direct action of glutathione both in vivo and in vitro to enhance intracellular magnesium and a clinical linkage between cellular magnesium, GSH/GSSG ratios, and tissue glucose metabolism.**

Barbagallo M, et.al. Effects of Glutathione on Red Blood Cell Intracellular Magnesium : Relation to Glucose Metabolism. Hypertension. 1999;34:76-82. doi: 10.1161/01.HYP.34.1.76

Glutathione and Oxidative Stress

Abstract

To **evaluate the relationship between oxidative stress and glucose metabolism**, insulin sensitivity and intraerythrocytic reduced glutathione (GSH)/oxidized glutathione (GSSG) ratio were measured in 10 non-insulin-dependent diabetes mellitus (NIDDM) patients and 10 healthy subjects before and after the intravenous administration of GSH. In particular, after baseline insulin sensitivity was assessed by a 2-hour euglycemic hyperinsulinemic clamp, either glutathione (1.35 g x m2 x min(-1)) or placebo (saline) were infused over a period of 1 hour.

In conclusion, our data support the hypothesis that abnormal intracellular GSH redox status plays an important role in reducing insulin sensitivity in NIDDM patients. Accordingly, intravenous GSH infusion significantly increased both intraerythrocytic GSH/GSSG ratio and total glucose uptake in the same patients.

De Mattia G, Bravi MC, Laurenti O, Cassone-Faldetta M, Armiento A, Ferri C, Balsano F. Influence of reduced glutathione infusion on glucose metabolism in patients with non-insulin-dependent diabetes mellitus. Metabolism. 1998 Aug;47(8):993-7. PMID: 9711998

The role of glutathione in tumor cells

- •Glutathione is an abundant natural tripeptide found within almost all cells. Glutathione is highly reactive and is often found conjugated to other molecules via its sulfhydryl moiety. It instils several vital roles within a cell including antioxidation, maintenance of the redox state, modulation of the immune response and detoxification of xenobiotics. **With respect to cancer, glutathione metabolism is able to play both protective and pathogenic roles. It is crucial in the removal and detoxification of carcinogens, and alterations in this pathway, can have a profound effect on cell survival.** However, by conferring resistance to a number of chemotherapeutic drugs, elevated levels of glutathione in tumour cells are able to protect such cells in bone marrow, breast, colon, larynx and lung cancers. Here we present a number of studies investigating the role of glutathione in promoting cancer, impeding chemotherapy, and the use of **glutathione modulation to enhance anti-neoplastic therapy.**
- Cell Biochem Funct. **2004** Nov-Dec;22(6):343-52.Balendiran GK, Dabur R, Fraser D.PMID:15386533

Pathophysiologic and Therapeutic roles of glutathione in carcinoma

- •Glutathione (GSH) is an important intracellular antioxidant that instills several vital roles within a cell including maintenance of the redox state, drug detoxification, and cellular protection from damage by free radicals, peroxides and toxins. Molecular alterations in the components of the GSH system in various tumors can lead to increased survival and enhanced tumor drug resistance. Early identification of the importance of intracellular GSH to detoxification reactions has now led to investigating the potential importance that GSH chemistry has on signal transduction, molecular regulation of cellular physiology and regulation of apoptosis pathway. Several therapeutic agents that target this system have been developed and used experimentally and clinically in an attempt to improve cancer chemotherapy. This review highlights different roles played by **GSH that finally regulate tumor growth and advances in the use of GSH-based drugs to specifically target this detoxifying system in cancer treatment as a means to increase therapeutic response and decrease chemotherapeutic drug resistance.**
- Singh S, Khan AR, Gupta AK., J Exp Ther Oncol. **2012**;9(4):303-16.PMID:22545423

Does GSH decrease after cancer treatment?

Conclusions:

A significant decline in GSH–glutathione disulfide, cysteine-cystine, and vitamin E status occurs after chemotherapy and BMT. Standard PN does not improve antioxidant status compared with administration of micronutrients alone.

Further evaluation of PN formulations to support patients undergoing high-dose chemotherapy and BMT are needed.

Am J Clin Nutr 2000;72:181–9.

GSH and Oxaliplatin

Conclusion: This study provides evidence that GSH is a promising drug for the prevention of oxaliplatin induced neuropathy, and that it does not reduce the clinical activity of oxaliplatin.

Cascinu S, et.al. Neuroprotective Effect of Reduced Glutathione on Oxaliplatin-Based Chemotherapy in Advanced Colorectal Cancer: A Randomized, Double-Blind, Placebo-Controlled Trial. J Clin Oncol 20:3478-3483.

GSH and Oxaliplatin

Abstract

In conclusion, this study indicates that coadministration of GSH is an effective strategy to reduce the oxaliplatin-induced neurotoxicity without impairing neither the pharmacokinetics of oxaliplatin, nor the Pt-DNA adduct formation.

Milla P, Airoldi M, Weber G, Drescher A, Jaehde U, Cattel L. Administration of reduced glutathione in FOLFOX4 adjuvant treatment for colorectal cancer: effect on oxaliplatin pharmacokinetics, Pt-DNA adduct formation, and neurotoxicity. Anticancer Drugs. 2009 Jun;20(5):396-402. PMID: 19287306

GSH and Normal Cell Repair after Radiation

The results indicate that GSH is involved in PLD repair and, in particular, in the repair of damage induced by radiation delivered under hypoxic conditions.

Midander J, Deschavanne PJ, Debieu D, Malaise EP, Revesz L. Reduced repair of potentially lethal radiation damage in glutathione synthetase-deficient human fibroblasts after X-irradiation. Int J Radiat Biol Relat Stud Phys Chem Med. 1986 Mar;49(3):403-13. PMID: 3485589

GSH levels and Radiation Protection

Abstract

Therefore, an increase in the level of endogenous GSH in lymphocytes was unable to reduce chromosomal damage induced by 3 Gy or above, whereas decrease in the level of GSH enhanced the frequency of CA at all radiation doses in a non-uniform manner. **It seems that GSH did not act as a radioprotector against DNA damage induced by higher dose X-rays rather it acts as a modulator of DNA repair activity.**

Pujari G, Berni A, Palitti F, Chatterjee A. Influence of glutathione levels on radiation-induced chromosomal DNA damage and repair in human peripheral lymphocytes. Mutat Res. 2009 Jun-Jul;677(1-2):109-10. PMID: 19386243

DMSO and Cancer Pain

- It is commonly used in combination with IVC and other agents to penetrate the PNS and CNS tissues (as well as others).

- Also shows promise in pain control.

Hoang BX, et.al. Dimethyl Sulfoxide–Sodium Bicarbonate Infusion for Palliative Care and Pain Relief in Patients With Metastatic Prostate Cancer. Journal of Pain & Palliative Care Pharmacotherapy. 2011;25:350–355. DOI: 10.3109/15360288.2011.606294

Prostate cancer (adenocarcinoma of the prostate) is the most widespread cancer in men. It causes significant suffering and mortality due to metastatic disease. The main therapy for metastatic prostate cancer (MPC) includes androgen manipulation, chemotherapy, and radiotherapy and/or radioisotopes. However, these therapeutic approaches are considered palliative at this stage, and their significant side effects can cause further decline in patients' quality of life and increase non–cancer-related morbidity/mortality. In this study, the authors have used the infusion of dimethyl sulfoxide–sodium bicarbonate (DMSO-SB) to treat 18 patients with MPC. The 90-day follow-up of the patients having undergone the proposed therapeutic regimen showed significant improvement in clinical symptoms, blood and biochemistry tests, and quality of life.

There were no major side effects from the treatment. In searching for new and better methods for palliative treatment and pain relief, this study strongly suggested therapy with DMSO-SB infusions could provide a rational alternative to conventional treatment for patients with MPC.

Hoang, et.al. Protocol:

Patients with pain score <3 points (VDS) were treated with infusion of 25 mL of 99.9% DMSO solution mixed with 250 mL of SB 1.4% solution and 10 mL of magnesium sulfate 1.5% (7 patients). Patients with pain score ≥3 points were treated with infusion of 40 mL DMSO mixed with 500 mL of SB 1.4% solution and 10 mL of magnesium sulfate 1.5% (11 patients).

Hoang, et.al. Protocol:

Patients with pain score that did not decrease in 3 days of treatment with infusion of 40 mL DMSO were recommended to receive a dose of 60 mL of DMSO mixed with 500 mL of SB 1.4% solution (2 patients). When the pain was completely under control, the dose of DMSO returned to 40 mL. The patients who were treated with 40 DMSO and achieved complete pain control had their dose of DMSO reduced by 5 mL after each cycle of infusion reaching a maintenance dose of 25 mL DMSO per day for the remaining cycles. The speed of drip was 40 to 60 drops per minute (mean: 50 drops per minute).

Hoang, et.al. Protocol:

- #1:
  - 42 mL 8.4% Bicarbonate
  - 208 mL Sterile Water
  - 25 mL 99% DMSO
  - 10 mL Magnesium Sulfate
  - 4 ml Potassium Chloride
- #2:
  - 83 mL 8.4% Bicarbonate
  - 417 mL Sterile Water
  - 40 mL 99% DMSO
  - 10 mL Magnesium Sulfate
  - 6 ml Potassium Chloride

Hoang, et.al. Protocol:

All patients received the full 12 cycles of five infusions. The patients with edema were treated with appropriate diuretics. Patients also were instructed to take 1000 mg of potassium orally if there was no evidence of kidney failure. During the treatment period, patients were allowed to take any medication, dietary supplements, vitamins, or herbs for any health disorders they were experiencing.

Hoang, et.al. Side effects:

- No high grade.
- There were nine episodes of transient mild headache and five episodes of moderate chilling during and after treatment. These side effects subsided and were resolved in 1 to 2 hours and all patients were able to continue with the next set of infusions. For these patients who experienced transient headache and episodes of chilling spell, we recommended slowing the drip rate to 30 drops per minute in the next infusion session.

Hoang, et.al. Outcomes:

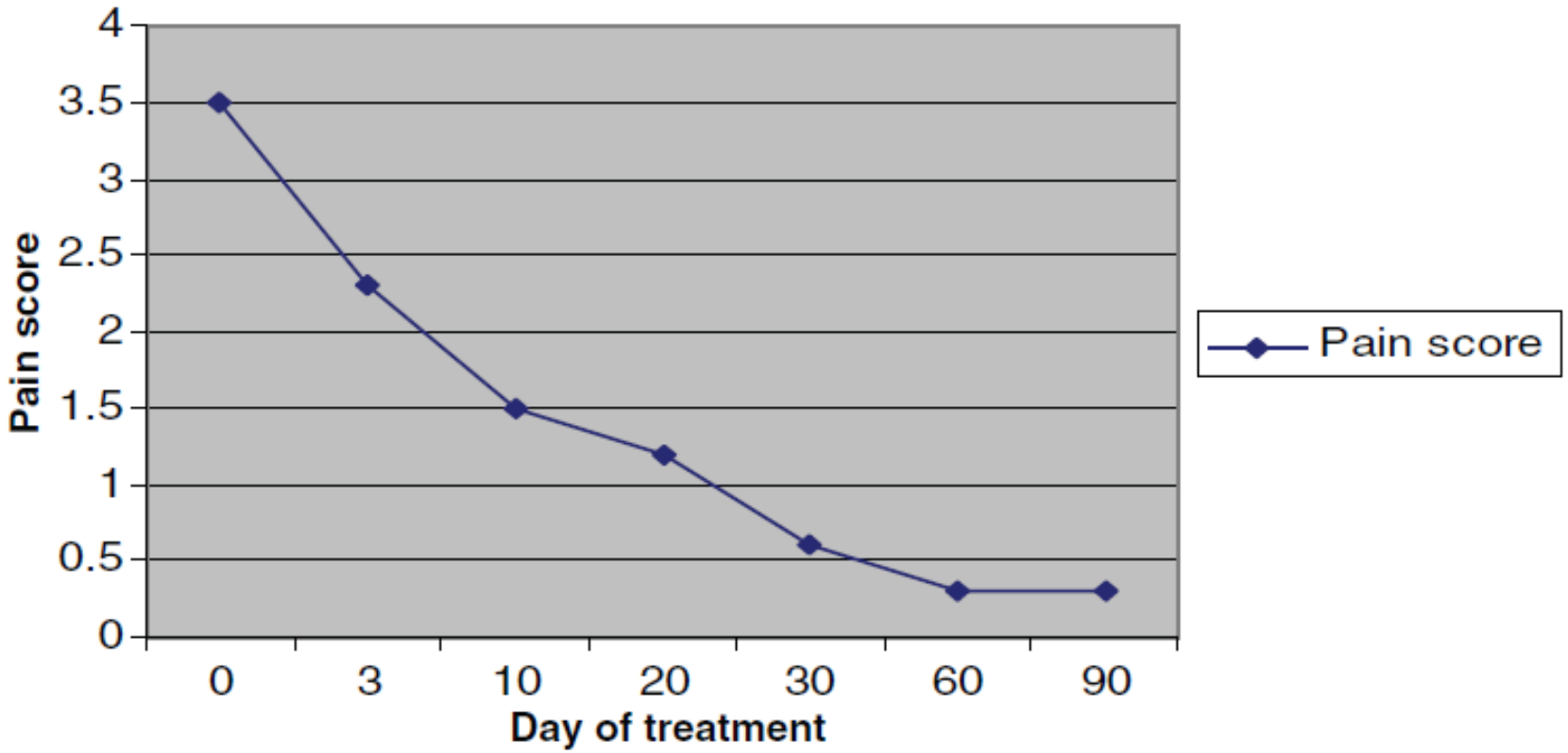


FIGURE 1. Reduction in pain from baseline during the treatment period.

Hoang, et.al. Conclusions:

“The results of this open-label clinical study suggest that patients with MPC can be treated effectively and safely with DMSO-SB infusion. These agents can be produced inexpensively and used for the patients in and out of the hospital. The patients with MPC who were treated with DMSO-SB infusion had fast relief in two of the key symptoms—pain and urination outflow limitation. More importantly, DMSO-SB treatment substantially improved the patients’ quality of life without major negative effects on body and organ functions.”

Nutrient Therapy

82 yo male with stage IV end stage pancreatic cancer

- Presents severely malnourished bed/wheelchair bound
- Children would just like nutritional support for quality of life.

- After first rehydration amino acid bag. Children report father is out the next day mowing the lawn.
- Continued therapy 2-3 times per week with nutritional support. Providing him with energy to continue higher quality of life for additional 6 weeks.