MedNut Mail

The How, When, Where, Which and Why of pharmacotnutrition

Vitamin C and sodium valproate

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https://medicationsandnutrition.online

Commentary

… *hSVCT1 (Sodium Vitamin C Transporter 1) expression and function were significantly decreased in intestinal epithelial cells by the histone deacetylase inhibitors (in Australia -* ***Vorinostat - Zolinza****), valproic acid, and sodium butyrate (NaB)* is part of a comment from a recent abstract (https://doi.org/10.1016/j.jnutbio.2021.108838). Effectively this means sodium valproate decreases vitamin C absorption.

As we are unable to produce it ourselves vitamin C is deemed an essential nutrient and as such has four main functions including -

1. **Co-factor in various enzymes** – including collagen synthesis, carnitine synthesis, catecholamine synthesis, cholesterol synthesis, synthesis of several hormones, neuropeptide amidation and release in the brain, tyrosine metabolism;
2. **Antioxidant** – regenerate α-tocopherol and CoQ10, effective scavenger of free radicals and other reactive oxygen and nitrogen species under physiological conditions ie protective against oxidative stress – refer Note 1. The brain utilizes 25% total body glucose which means high oxidative metabolism that necessitates protective antioxidants; the brain preferentially retains vitamin C at the expense of all other tissues. Neurodegeneration occurs when there is sustained high oxidative stress such that all available vitamin C in the brain is consumed, resulting in no available vitamin C to modulate neuronal metabolism.
3. **Pro-oxidant** – may increase Reactive Oxygen Species (ROS) in cells via dihydrogen peroxide. This pro-oxidant activity of vitamin C leads to the breakage of cellular DNA that interrupts the redox balance and eventually alters cellular metabolism such as energy metabolism through NAD depletion.
4. **Other** – changes ferric to ferrous and thus increases iron absorption in the duodenum, down-regulates HIF 1α (associated with low oxygen environments), recycles α-tocopherol in the lipid bilayers and in erythrocytes, prevents glutamate-induced cell damage and death, and other functions.

The three main transport mechanisms for vitamin C include -

1. **SVCT1 – sodium vitamin C transporter 1**

- tissue distribution - apical brush border membranes of the intestines, renal tubular cells, liver, lungs and skin,

- primary functions are to enhance intestinal absorption and renal reabsorption of vitamin C and to regulate intestinal vitamin C uptake. Megadoses of vitamin C (> 1 g) are less effective than 250-500 mg doses several times per day;

2. **SVCT 2 – sodium vitamin C transporter 2 –**

- tissue distribution - found in most other tissues, and especially brain, placenta, retina, bone,
- primary functions are to transport vitamin C from cytosol into the mitochondrial matrix, preserve intracellular vitamin C status, and to regulate vitamin C uptake and neuronal content; not present in astrocytes however oxidative stress can induce SVCT2 in astrocytes and increase their expression in neurons,
- is a Ca(2+)/Mg(2+)-dependent transporter ie when Ca^{2+} and Mg^{2+} are absent, the SVCT2 transport system is in an inactive form (refer Note 2),
- expression inhibited by TNF-α and IL-1β which suggest SVCT2 may be regulated by the inflammatory response; TNF-α is elevated in the presence of low B12.

3. **GLUT – primarily transports glucose into cells**

- Glut 1 + Glut 3 transport DHA (dehydroascorbic acid) into neurons and glial cells. This route is plan B for increasing vitamin C in neurons.

The main factors that affect the bioavailability of vitamin C are the absorption rate at the intestinal level and renal re-absorption rate. Inadequate vitamin C status manifests as -

- classic - impaired wound healing, gingivitis, perifollicular haemorrhages, ecchymoses, petechiae, eg scurvy,
- non-classic - malaise, fatigue and lethargy – may be partially due to reduced levels of carnitine and reduced synthesis of epinephrine.

One of the mechanisms by which sodium valproate decreases carnitine availability is inhibition of endogenous carnitine production. Sodium valproate's inhibition of vitamin C absorption is one of the likely mechanisms as insufficient vitamin C means the body cannot produce adequate carnitine.

There are some populations that are at particular risk of carnitine deficiency due to sodium valproate-induced vitamin C inadequacy, including –

- **Vegans** - the primary source of carnitine is from the conversion of lysine to carnitine - vitamin C is essential in this process and sodium valproate reduces vitamin C availability. Both carnitine and vitamin C interventions are probably advisable.
- **Limited animal food intake** – as the animal food intake reduces so the dependency on the production of

carnitine from the lysine + vitamin C pathway increases; reduced vitamin C availability means a likely limited production of carnitine that may not meet body requirements.
- **Enteral + parenteral feeds** - do these formulas contain adequate vitamin C to compensate for the reduced vitamin C uptake induced by sodium valproate? Further do these formulas contain adequate carnitine?

What interventions will you initiate when sodium valproate is prescribed - will you –

- request vitamin C status and magnesium levels be clarified?
- recommend prophylactic vitamin C and magnesium interventions?
- ensure vitamin C and magnesium interventions are administered at a different time from sodium valproate?
- check that other prescribed medications do not also negatively impact vitamin C status and magnesium levels?
- ensure the maximum individual dose for the vitamin C intervention is not more than 500 mg?

Conclusions

The negative impact of sodium valproate on nutritional factors is significant and has ongoing consequences for the consumer, particularly those who do not consume animal foods or only consume them in very limited quantities. The inclusion of vitamin C, magnesium and carnitine in management strategies has the dual benefits of reducing side effects and improving outcomes for the consumer.

Note 1. Oxidative Stress

Results from an imbalance between the levels of ROS and endogenous antioxidant mechanisms which causes structural and functional impairment of cells by degrading lipids, proteins, and nucleic acids, and ultimately results in cell death.

Antioxidants neutralize or quench the action of reactive substances, and include CoQ10, alpha tocopheral, vitamin C, vitamin A, pyridoxine, selenium, zinc, carnosine, riboflavin, and others.

Note 2 - Magnesium ion supplementation
(DOI:10.1016/j.tranon.2019.10.017)

Both MgSO4 and MgCl2 were found to increase the vitamin C uptake activity of SVCT-2 in both cells with high and low SVCT2 levels.

The inclusion of magnesium with the vitamin C intervention resulted in increased ROS generation via dihydrogen peroxide. This pro-oxidant activity of vitamin C led to the breakage of cellular DNA which interrupted the redox balance and eventually altered cellular metabolism such as energy metabolism through NAD depletion.

Case study

Medical History with Nutritional Aspect

Amputation	☐	Constipation	☐	Dysphagia	☐	MND	☐
Anaemia	☐	CVA	☐	Enteral Feed	☐	MS	☐
Arthritis	☐	CVD	☐	Falls	☐	Osteoporosis	☐
Cancer	☐	Dementia	☐	Fracture	☐	PD	☐
CCF	☐	Dentures	☐	Frailty	☐	Pressure Area	☐
Chest Infection	☐	Depression	☐	Gout	☐	Renal	☐
COAD	☐	DM Type 1	☐	Hypertension	☐	Ulcer	☐
Confusion	☐	DM Type 2	☐	Incontinent	☐	UTI	☐

Food Allergies: hypercholesterolaemia

Other: haemorrhoids, Intellectual Disability

Biochemistry with Pharmaconutritional Consequences

Na:		mmol/l	Hb:		g/L	Albumin:		g/L	BSL:		mmol/l
K:		mmol/l	Lymph:			Total Protein:		g/L	HbA1C:		
Urea:		mmol/l	MCV:		mmol/l	B12:		mmol/L	INR:		
Creatinine:		mmol/l	Zn:		umol/l	Folate:		mmol/L	TSH:		mIU/L

Other: vit D 56, chol 7.4, Tg 1.5

Medications That May Adversely Affect Nutritional Status

Drug	Vits + Mins	bpp	>90%	N/V	C/D	Wt	App	Tst	Thir	Sal	Drlg	d m	Dys	BSL
METAMUCIL	Mg, Zn, Ca, B2		☐	NV	D		↓	☐				☐	☐	☐
PARACETAMOL			☐	NV	C		↓	☐				☑	☐	☐
			▩					▩				▩	▩	▩

Comments – medication and nutrition impacts (direct and indirect) only

Recent relevant biochemistry indicates

- elevated cholesterol – may be advisable to consider a drug intervention.

Dietary levels of caffeine intake in conjunction with drug inhibit antinocieception

Concurrent ingestion of paracetamol and iron resulted in increased rate of iron absorption and decreased extent of drug absorption; there is a recommendation that paracetamol and iron be administered at different times from each other.

Mr ABA is a tall, well-built, slender, pleasant, polite man who was holding the door open for the residents whilst doing his daily lap around the building - he looks good.

Mr ABA is a resident because another family member is also a resident in the same facility and there is no-one else to care for him.

What else would you include?

Medications have profoundly and positively changed health outcomes however they do generally come with some nutritional harms. By identifying and addressing the nutritional harms, optimal health outcomes are closer to being achieved.

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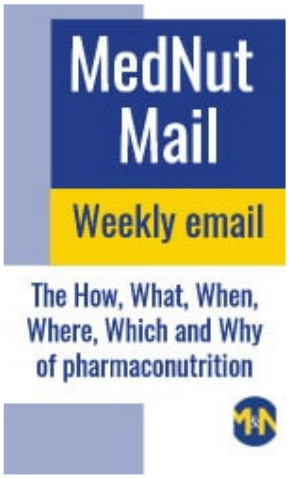

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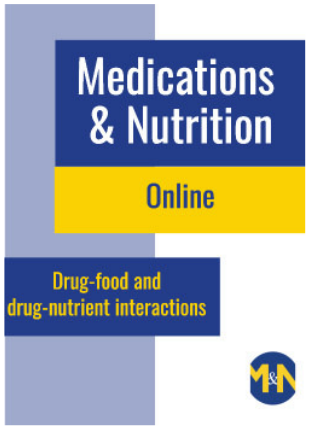

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