MedNut Mail

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

Pantothenate and pharmaconutriton

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Commentary

A nutrient that is very out-of-sight and out-of-mind is pantothenate – is there, or should there be, a pharmaconutrition concern?

Pantothenate is a B vitamin that is important -

- as the precursor for production of Coenzyme A (CoA or CoA-SH),
- in the synthesis of acyl carrier proteins essential in fatty acid biosynthesis,
- in the synthesis of pantethine, a naturally occurring physiological substance derived from pantothenate,
- in triggering immune cells to produce cytokines,
- in T cell polarization, bioenergetics, and anti-tumour immunity,
- in helping prevent cisplatin-induced deafness in guinea pigs when both drugs are administered jointly. When deafness has been previously caused by cisplatin, recovery sometimes occurs after the administration of pantothenic acid.

  CoA is important in cellular metabolism in all living organisms as it is an essential co-factor, particularly in activating carboxylic acids involved in both catabolic and anabolic reactions, including -

- chemical reactions that generate energy from fat, carbohydrates, protein and breakdown of ethanol;
- biosynthesis of fatty acids (necessary for biosynthesis of triacylglycerols, phospholipids, sphingolipids), cholesterol, acetylcholine, prenyl moieties (one or more hydrophobic molecules are added to a protein or chemical compound to facilitate attachment to cell membranes), bile acids, ketone bodies, haem, melatonin, glycosaminoglycans, glycoproteins, gangliosides, proteoglycans, etc;
- oxidation of fatty acids. A process that occurs in the mitochondria and that results in the conversion of fatty acids to acetyl-CoA;
- biosynthesis of amino acids and protein acylation;
- regulating metabolism – directly by allosteric regulation of pyruvate dehydrogenase kinase-PD K, carnitine palmitoyl transferase 1—CPT1, and indirectly by regulation of carbamoyl phosphate synthetase I;
- functioning as an acyl group carrier and a carbonyl-activating group in diverse biochemical reactions;
- gene expression and regulation such as protein and histone acetylation;
- neurotransmitter synthesis;
- cellular metabolic and signalling pathways;
- T cell polarization, bioenergetics, and anti-tumour immunity;
- mediating the citric acid cycle;
- detoxification reactions during which compounds are formed and then excreted in urine, eg hippuric or mercapturic acids;

- being an antioxidant in the oxidative and metabolic stress response;
- production of the free CoA protein CoAlation (cellular proteins that are modified by covalent attachment of CoA to cysteine thiols) - a process related to redox regulation and antioxidant defense;
- the formation of acyl groups both during the metabolism of glucose, amino acids and fatty acids in human cells and by those produced by gut microbiota, to form derivatives such as acetyl-CoA, succinyl-CoA, propionyl-CoA, isovaleryl-CoA, isobutyryl-CoA, α-methylbutyryl-CoA, β-hydroxy β-methylglutaryl-CoA aka HMG- CoA (a substrate for cholesterol and ketone bodies synthesis), malonyl-CoA (a substrate for lipogenesis and regulator of fatty acid oxidation), and fatty acyl-CoA (commonly referred to as acyl-CoA), e.g., palmitoyl-, oleoyl-, and stearoyl-CoA;
- itaconate – is an important intermediate metabolite isolated in the tricarboxylic acid cycle and is a key autocrine regulatory component involved in the development and progression of inflammation and immunity. Itaconate derivative itaconyl-CoA inhibits B12- dependent methylmalonyl-CoA mutase by an unknown mechanism;
- muscle metabolism - plasma concentration of pantothenate increases with exercise;
- malarial activity – CoA is higher in malarial erythrocytes than in normal erythrocytes; although malarial parasites can independently produce CoA they require an exogenous supply of pantothenate for survival;
- higher CoA levels in the liver and heart of diabetic rats and mice than in healthy rats and mice;
- butyrate β-oxidation for colonocyte energy metabolism;
- a possible association with the development of colitis, some cancers and diabetes.

CoA biosynthesis is upregulated in response to oxidative stress and serum starvation, and downregulated by growth factor signalling.

Changes in the CoA/acetyl-CoA ratio affect the regulation of energy metabolism and other cellular processes, such as autophagy, mitosis, and cell death.

Pantothenate sources

The main sources of pantothenate include -

(a) **food**,

(b) **gut microbiota**. Pantothenic acid is synthesized by bacteria in the colon (large intestine), converted to CoA, distributed similarly to dietary pantothenate, and is directly absorbed. Intestinal commensal bacteria that can produce pantothenate include Bacteroides fragilis and Prevotella copri (Bacteroidetes); some Ruminococcus spp. (R. lactaris and R. torques) (Firmicutes); Salmonella enterica and Helicobacter pylori (Proteobacteria) whilst some (intestinal commensal bacteria) have pantothenic acid transporters and may compete with the

host for access to pantothenate - examples include Fusobacterium (Fusobacteria) and Bifidobacterium spp. (Actinobacteria) and some strains of Clostridium difficile, Faecalibacterium spp., and Lactobacillus spp. (Firmicutes),

(c) **recycled cellular content**.

Deficiency

Naturally occurring pantothenic acid deficiency in humans is very rare and has been observed only in cases of severe malnutrition.

- human evidence includes headache, listlessness, fatigue, insomnia, intestinal disturbances, and numbness, burning and tingling in hands and feet;
- animal evidence includes damage to the adrenal glands, anaemia due to decreased synthesis of haem, low blood glucose, rapid breathing and heart rates, convulsions, skin irritation, feather abnormalities, spinal nerve damage associated with the degeneration of the myelin sheath, decreased exercise tolerance and diminished storage of glucose (in the form of glycogen) in muscle and liver, and greying of the fur.

The diversity of symptoms emphasizes the numerous functions of pantothenic acid in its coenzyme forms.

Unfortunately, the deficiency symptoms are shared with many other nutrients and consequently pantothenate deficiency is not really uniquely identifiable by symptoms.

Known transporters

- **SMVT** (sodium-dependent multivitamin transporter) - transports pantothenate from intestine to epithelium, from the proximal tubules in the kidneys (reabsorption), and across the Blood Brain Barrier into the brain.
- **OAT1** - transports pantothenate from blood into kidneys.

Pantothenate-drug interactions

Azathioprine

- metabolised to mercaptopurine which is a pantothenic acid antagonist.

Carbamazepine

- - competitively inhibits pantothenic acid absorption. This suggests carbamazepine utilises the SMVT transporter however there does not seem to be any direct research to clarify this point.

Probenecid

- decreases urinary excretion of pantothenic acid – likely mechanism OAT1 inhibition.

Sodium valproate

- reacts with acetyl-CoA to cross the outer mitochondrial membrane and then reacts with carnitine to cross the inner mitochondrial membrane to undergo beta-oxidation in the mitochondria; shortages of either

of the reactants will decrease beta-oxidation of the drug,
- some evidence indicates current administration of carnitine and pantothenate interventions may prevent some drug-induced adverse effects.

Potential pantothenate-drug interactions

These are potential interactions because they are highly likely but have not been tested – SMVT inhibitors are likely to decrease pantothenate absorption which means reduced availability of pantothenate, whilst OAT1/3 inhibitors decrease renal uptake of pantothenate which means pantothenate remains in the blood for a longer duration and therefore, if elevated, could manifest with unacceptable side effects.

Some SMVT inhibitors

- includes ketoprofen, diclofenac, ibuprofen, phenylbutazone, flurbiprofen, etc,
- salicylic acid and indomethacin found to have concentration ranges that correspond to the clinically relevant unbound concentrations in plasma.

Some OAT1/3 inhibitors

- includes probenecid, novobiocin, rifampicin, tenofovir, cabotegravir, etc.

Given the profound positive impact of pantothenate on physiological function, it seems strange to me that so few prescribed medications have been identified that interact with this nutrient. Exacerbating the issue is the lack of awareness of pantothenate's profoundly important physiological role and the consequent lack of routine testing of its status.

What interventions will you initiate when you see someone prescribed a drug that interacts with pantothenate or inhibits OAT1/3 transporters – will you -

- request pantothenate status be clarified?
- review dietary intake for known identified OAT1/3 involvement?
- check for mercury exposure and levels?

Conclusions

Pantothenate has a powerful role and alteration to its status has significant implications for body function therefore there should be concern regarding pharmaconutrition implications.

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: colostomy

Other: Ca bowel + prostate + skin, hypercholesterolaemia

Biochemistry with Pharmaconutritional Consequences

No recent relevant results available that may have a pharmaconutrition component.

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
Allopurinol			☐	NV	D			☑				☐	☐	☐
Cholecalciferol	(1/day)		☐					☐				☐	☐	☐
MOVICOL			☐	N	D			☐				☐	☐	☐
Pantoprazole	(40 mg/day) B1, B12, Ca, Fe,		☑	NV	CD		↓	☑				☑	☐	☐
Perindopril			☐	NV	D			☑				☑	☐	☐
Thyroxine	(100 mcg/day) A, Ca, carnitin		☑	V	D	↓		☐				☐	☐	☑
Venlafaxine			☐	NV	CD	↕	↓	☑				☑	☐	☐
			▩					▩				▩	▩	▩

Extra drug: enprocal qid

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

No recent relevant biochemistry available. The plasma proteins are the primary transporters for two of the prescribed drugs and hypoproteinaemia may alter their effects and expression of their side effects.

Side effects for 4 of the prescribed drugs include nausea, vomiting and altered taste, and diarrhoea is a side effect of 5 of the prescribed drugs.

Therapeutic pantoprazole doses increase gastric pH > 4, pepsin can only digest proteins within the pH range 1.8-3.2 consequently proteins remain intact, able to cross into the blood stream and promote IgE antibodies, and subsequent allergenic response.

Longterm PPI use such as pantoprazole alters gut microbiome by increasing in Fimicutes and reducing Bacteriodetes.

Prescribed 3 drugs that may alter glycaemic status, being allopurinol, perindopril and thyroxine.

Pantoprazole decreases B12, vitamin C, magnesium, zinc and iron absorption, may decrease calcium absorption, and decreases thiamine availability.

Thyroxine increases urinary excretion of carnitine.

Currently prescribed vitamin D (1 tab/day) therefore advisable to check vitamin D levels and if still low then review current vitamin D management strategy.

Prescription of pantoprazole indicates prudent clinical practice for B12 management as outlined -

- establish B12 status at commencement of drug treatment, and monitor on a regular basis, or
- commence a prophylactic B12 intervention with oral supplements as they are not protein-bound and therefore do not require gastric acidity for absorption.

There is increasing evidence that proton pump inhibitors such as pantoprazole significantly impair magnesium absorption - magnesium deficiency manifests as confusion, disorientation, personality changes, loss of appetite, depression, muscle cramps, tingling, numbness, hypertension, cardiac dysrhythmia, seizures. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status. Cellular magnesium status is unknown whilst magnesium levels within acceptable range however if magnesium levels are low then typically indicates significant cellular depletion and intervention recommended.

Prescribed 2 drugs that alter zinc status, being pantoprazole and perindopril therefore advisable to clarify zinc status.

Bowels –

- regular aperient prescribed,

- oral PRN aperient prescribed.

Mr ABN has been losing weight for the last few months whilst staff advise very good appetite.

Mr ABN is a slender pale man with cool hands and who was sitting in the Day Room when I went to speak to him - he told me he eats well but does not sleep well, and that he does not go outside even on nice sunny days.

Since Mr ABN is pale, advisable to check iron levels and if low then short term (90-120 days) intervention recommended. Evidence indicates iron deficiency anaemia is unlikely to resolve if oral iron interventions are administered whilst a proton pump inhibitor is prescribed therefore advisable to consider a non-oral iron intervention.

Historically Mr ABN was prescribed B12 injections therefore advisable to check status and if low then advisable to consider intervention.

Mr ABN is currently prescribed thyroxine and is losing weight therefore at risk of overmedication. Both pantoprazole and a nutrition support product intervention decrease thyroxine absorption. Advisable to –

- review necessity for proton pump inhibitor prescription,
- review administration time of the nutrition support product,
- check thyroid function.

Mr ABN has been prescribed a proton pump inhibitor for at least 2 years and likely longer. There is increasing evidence that longterm (3+ years) proton pump inhibitor prescription is associated with -

- altered gut microbiome;
- increased risk of food sensitivities at a level of peanut allergy, due to partial protein digestion;
- increased risk of coeliac disease due to partial protein digestion;
- increased risk of scurvy;
- generalised malnutrition due to impaired absorption of a range of nutrients such as B12, vitamin C, magnesium, zinc, iron, etc;
- altered gastric pH which reduces absorption dynamics of a range of drugs and nutrients. Altered drug availability is relatively easily identified however reduced nutrient absorption is rarely identified due to the non-specific nature of their signs and symptoms.

Consequently advisable to reconsider reviewing current proton pump inhibitor prescription and consider -

- whether proton pump inhibitor prescription is still required;
- if suppression of gastric acidity is still required then could it be managed with an H2 antagonist such as ranitidine (there is a general belief that they cause less nutritional harm than proton pump inhibitors).

If thyroxine dose changed and weight loss consequently ceases then advisable to review necessity for continued prescription of the nutrition support product.

Salicylates are OAT2 substrates therefore there is likely competition

with allopurinol for transport from blood into kidneys. Foodstuffs containing salicylates include -

- *very high levels* - vegetables such as broad bean, cauliflower, broccoli, mushroom, spinach, tomato; fruits such as grapefruit, orange, pineapple, grape, plum, dried fruits; some processed meat products such as devon, meat pies, sausages; alcoholic beverages such as beer, wine, port, brandy; herbs, spices and condiments;
- *high levels* - vegetables such as capsicum, corn, cucumber, onion, zucchini; fruits such as apples, apricots, cherries, nectarines, peaches, watermelon; vegetable oils such as olive, coconut, walnut; nuts and snackfoods.

Pantoprazole inhibits thiamine uptake by liver, kidney and muscles which means thiamine remains in the blood for longer.

Note - Longterm PPI use such as pantoprazole alters gut microbiome by increasing in Fimicutes and reducing Bacteriodetes. In this case study this means Fimicutes is decreasing pantothenate availability because there is competition with the host for pantothenate uptake, whilst Bacteriodetes is producing pantothenate that is available for host and other microbiota to absorb – net pantothenate available is anyone's guess.

What else would you include?

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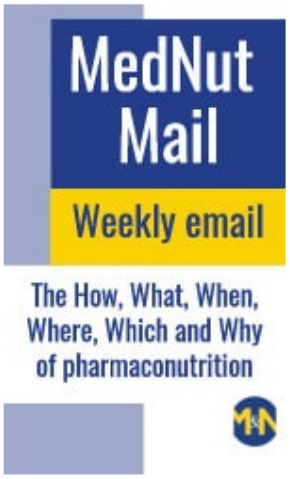

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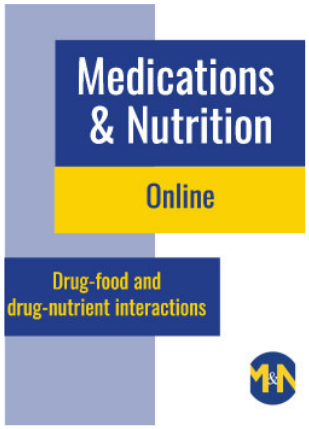

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