MedNut Mail

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

Pyridoxine and pharmaconutrition

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Commentary

Vitamin B6 (pyridoxine) is important in many body functions and is seemingly now becoming “sexy” to some in the research world …

Functions

B6 has many roles within the cell

- as a cofactor in several one-carbon metabolic processes,
- as a coenzyme it is important in 150+ biochemical reactions,
- as an antioxidant and is similarly as effective as the anti-oxidants vitamins C and E,
- as a modifier of the expression and action of steroid hormone receptors,
- protein, amino acid and polyamine metabolism,
- carbohydrate and lipid metabolism,
- neurotransmitter metabolism,
- cellular signalling,
- mitochondrial function,
- erythropoiesis,
- supports the immune system,
- as an anti-epileptic by antagonising ATP at the P2X7 receptors,
- for conversion of tryptophan to niacin,
- speculatively that infants develop mechanisms to protect the brain from B6 deficiency and thus B6 deficiency in adults is expressed in the peripheral nerves.

Sources

- diet
- gut microbiota
- renal resorption

Absorption

B6 is in a phospborylated form when consumed, is dephosphorylated in the intestinal brush border in the jejunum for absorption, and then phosphorylated again for distribution.

Pyridoxine deficiency

B6 deficiency may occur in those with uraemia, cirrhosis, older age, malnutrition, atherosclerosis and cerebrovascular diseases, neurodegenerative diseases, renal insufficiency, dialysis, gastro-intestinal diseases, hyperhomocysteinaemia, alcoholism, niacin deficiency, macular degeneration, smokers, likely others.

Symptoms include

- neurologic symptoms that include somnolence, confusion, and neuropathy; neuropathy is characterized by numbness and pain and later atrophy and weakness, absent distal reflexes, sensory loss to all modalities; electrophysiologic studies show it is predominantly axonal,
- skin changes that include seborrheic dermatitis, atrophic

glossitis with ulceration, angular cheilitis, conjunctivitis, intertrigo, and a pellagra-like eruption,
- microcytic anaemia - reflects decreased haemoglobin synthesis,
- epileptic convulsions,
- depression,
- Parkinson's disease,
- impaired cognitive function,
- reduced humoral and cellular immune response,
- impaired tryptophan metabolism.

Pyridoxine excess

Excess levels disproportionately affect the large sensory fibres, causing numbness and sensory ataxia, loss of vibration and proprioception with absent reflexes, and positive Romberg (positive result is when a person is unable to maintain balance with their eyes closed).

Excess intake seems to range from 10 mg/day up to 2 g/day.

Symptoms can develop from 1 month to 3 years after initiating pyridoxine interventions.

Transporters

OAT1/3 transporters are identified by the FDA (Food and Drug Administration) as transporters that are likely to play a significant role in drug-drug interactions and consequently are now a part of the drug discovery process.

- Blood into kidneys – OAT1/3,
- Kidneys into urine – speculation includes OAT4, MATE1, P-gp, MRP2, MRP4, MATE2K, or BCRP,
- Urine to blood - studies suggest OAT4 may have a role.

Carriers - mainly bound to albumin in plasma, and haemoglobin in erythrocytes.

B6-drug interactions

Carbamazepine

Carbidopa + Levodopa

Celecoxib

Diclofenac

Estradiol + Norethisterone

Ethinyloestradiol + Norethisterone

Hydralazine

Isoniazid

Lamotrigine

Levetiracetam

Meloxicam

Mestranol + Norethisterone

Norethisterone

Penicillamine

Phenelzine

Phenobarbitone

Phenytoin

Primidone

Sodium valproate

Sulindac

Topiramate

Tranylcypromine

Potential B6-drug interactions

Are likely when prescribed medications that are substrates and/or inhibitors of the OAT1/3 transporters.

We don't know the duration of inhibition of the prescribed medications of foodstuffs that inhibit OAT1/3 transporters, and whether the durations between drugs are of a similar period, so it is difficult to identify a time that has a minimal inhibition impact.

Further, if OAT1/3 inhibition is resulting in sustained elevated B6 levels, then are the elevated B6 levels a significant cause of peripheral neuropathy? And how do we lower those elevated B6 levels without causing a B6 deficiency?

What actions will you initiate when you see someone whose prescribed medications negatively impact B6 status – will you -

- request B6 status be clarified?
- exclude obvious dietary and nutrient supplement intake if B6 elevated?
- peruse prescribed medications for inhibitory impacts on the OAT1/3 transporters?
- peruse preferred foodstuffs for inhibitory impacts on the OAT1/3 transporters?
- start considering elevated pyridoxine as a significant health issue?
- start moving B6 up your key nutrients list?
- specifically start checking B6 status in smokers?

Conclusions

Given the importance of B6 in so many aspects of body function, and given the increasing number of prescribed medications that inhibit its renal uptake, are we already seeing B6 deficiency and/or excess without recognizing it?

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: GORD, epilepsy, shingles cholecystectomy, CLL

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
Carbamazepine	B6, biotin, carnitine, D, folate,	☐	NV	CD	↑	↑	☑				☑	☐	☐
Cholecalciferol	(1/day)	☐					☐				☐	☐	☐
Rabeprazole	(20 mg/day) B1, B12, Ca, Fe,	☑	NV	CD	↑	↓	☑				☑	☐	☐
Venlafaxine		☐	NV	CD	↕	↓	☑				☑	☐	☐
Warfarin	D	☑	NV	D			☑				☐	☐	☐
		▩					▩				▩	▩	▩

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

No recent relevant biochemistry available. Advisable to check plasma proteins (albumin, total proteins) as markers of nutritional status. The plasma proteins are the primary transporters for two of the prescribed drugs and hypoproteinaemia may alter their effects.

Carbamazepine decreases absorption of carnitine and biotin and decreases availability of folate and vitamin D.

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

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

There is increasing evidence that proton pump inhibitors such as rabeprazole 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. Advisable to check magnesium status.

Bowels –

- no regular interventions prescribed,
- no PRN interventions administered,
- no Nurse Initiated interventions administered.

Staff advise Mr ABP eats well.

Mr ABP has been prescribed a proton pump inhibitor since admission ie 3 years and likely before then. There is increasing evidence that longterm (3+ years) proton pump inhibitor prescription is associated with -

- increased risk of dementia;
- 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).

Mr ABP is at risk of developing diabetes because -

- carbamazepine competes with biotin for absorption and is preferentially absorbed at the expense of biotin status; evidence indicates biotin is important in a number of steps in carbohydrate metabolism. A short term (90-120 days) intervention of biotin 2 mg/day is likely to confer longterm benefit and is not associated with harm;
- evidence indicates TNF- α has systemic effects that result in insulin resistance and NIDDM; low B12 status exacerbates elevated TNF- α and he is currently prescribed rabeprazole which decreases B12 absorption therefore advisable to check B12 status;
- magnesium is important in glycaemic control and he is currently prescribed rabeprazole which significantly decreases magnesium absorption. 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.

Mr ABP is at risk of vitamin K deficiency because carbamazepine decreases vitamin K absorption plus he is prescribed warfarin with its vitamin K dietary restriction. Vitamin K is important in a range of body functions including bone health, the coagulation cascade and glycaemic control.

Several of Mr ABP's diagnoses fall within the dysfunctional mitochondria umbrella.

Mr ABP's diagnoses include shingles however whether that is a recent diagnosis is unclear. Zinc has a very important role in the immune system, therefore advisable to check zinc status and if low then consider a short term (90-120 days) intervention. However, rabeprazole is prescribed therefore effectiveness of an oral zinc intervention is likely to be limited.

Longterm prescription of a proton pump inhibitor such as rabeprazole is associated with both lower baseline zinc stores and an incapability of adequately increasing zinc plasma levels with oral zinc supplements; authors speculate the effect is likely drug class rather than specific drug.

Mr ABP's diagnoses include hypercholesterolaemia. There are many factors that cause

hypercholesterolaemia however Mr ABP is prescribed 2 medications, being carbamazepine and venlafaxine, that include hypercholesterolaemia as a side effect therefore advisable to monitor cholesterol status on a regular basis.

Mr ABP's prescribed 3 medications being carbamazepine, rabeprazole and venlafaxine, that include hyponatraemia as a side effect. Hyponatraemia is associated with increased risk of falls and poor appetite.

Venlafaxine may interact with tryptophan with negative consequences – mechanism of action is unclear.

Rabeprazole inhibits the thiamine and choline transporters OCT1 (into liver), OCT2 (into kidneys), OCT3 (into skeletal muscles).

What else would you include?

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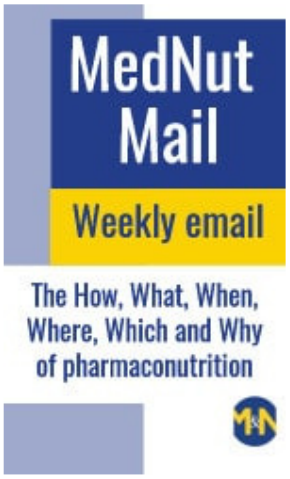

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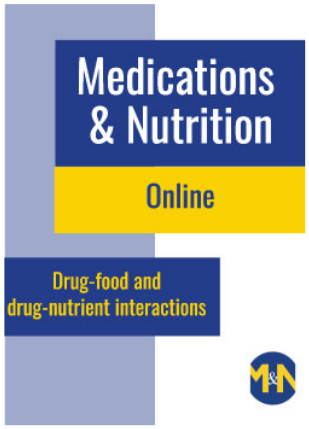

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