MedNut Mail

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

Metformin and vitamin B6 – Update 2023

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https://medicationsandnutrition.online

Editorial

Aspects of pyridoxine and pharmaconutrition have been written about in previous posts –

- Metformin & B6
- Elevated pyridoxine and pharmaconutrition
- B6 absorption requires an acid environment
- Pyridoxine and pharmaconutrition

This post is a summary and update with a focus on metformin's negative impacts on pyridoxine.

Summarized functions

Vitamin B6 is a generic name for about 6 different compounds and is important in a range of functions including mitochondrial function, antioxidant, gluconeogenesis and glycogenolysis, conversion of tryptophan to niacin, metabolism of one-carbon units, haemoglobin formation, immune function, neurological development and function, cellular signalling, limited evidence that pyridoxine enhances magnesium concentrations in blood and red blood cells.

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, riboflavin deficiency, macular degeneration, smokers, likely others.

Symptoms include

- impaired tryptophan metabolism,
- microcytic anaemia – due to decreased haemoglobin synthesis,
- reduced humoral and cellular immune response,
- neurologic symptoms including somnolence, confusion, epileptic convulsions, Parkinson's disease, impaired cognitive function, neuropathy, etc,

- skin changes including seborrheic dermatitis, atrophic glossitis with ulceration, angular cheilitis, conjunctivitis, intertrigo, pellagra-like eruption, etc,
- depression.

Pyridoxine excess

Early evidence suggests elevated B6 may be a common occurrence in those with kidney transplants. There are 2 papers in which the first study arbitrarily attributed the hyperpyridoxaemia to excessive dietary intake, whilst the second study included dietary intake in their study protocol and found there was not an excessive dietary intake of B6.

Excess levels of pyridoxine disproportionately affect the large sensory fibres and cause 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 and symptoms can develop from 1 month to 3 years after initiating pyridoxine interventions.

Homeostasis

Pyridoxine homeostasis reflects the balance between -

(i) dietary intake,

(ii) gut microbiota production,

(iii) renal reabsorption.

Pyridoxine requires an acidic environment for absorption and the small intestine has an acidic surface microclimate.

Pyridoxine transporters

- Gut to epithelium - ThTr1/2 (Thiamine Transporters 1/2),
- From the lysosomal lumen to the cytosol in the intracellular environment (a pyridoxine exporter) – DIRC2 (Disrupted in renal carcinoma 2).

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

Metformin and B6

Metformin negatively impacts vitamin B6 by -

- inhibiting absorption – metformin is both a substrate and an inhibitor of ThTr2 (Thiamine Transporter 2),
- inhibiting activation – metformin decreases riboflavin availability and thereby increases risk of B6 deficiency as riboflavin is essential for B6 activation,
- other mechanisms – it is likely metformin interferes with B6 availability via a number of other mechanisms such as the trans-membrane transporters – however they are proving difficult to identify.

Questions

What actions will you initiate when you see someone whose prescribed medications include metformin – will you -

- request B6 status be clarified?
- recommend regular monitoring of pyridoxine status whilst metformin is prescribed to clarify if there are any trends?
- if B6 is low then check riboflavin status ie use B6 status as an indirect marker of riboflavin status?

Conclusions

Given metformin is the fourth most commonly prescribed drug in the world it is surprising its negative impact on B6 status is only now attracting research interest.

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: sigmoid colectomy -> colostomy, hyperlipidaemia

Other: paraplegia, urosepsis, CKD, GORD, IDC

Biochemistry with Pharmaconutritional Consequences

No recent relevant results available.

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
Amlodipine			☑	NV	CD	↕	↕	☑				☑	☑	☐
Aspirin	C, Fe		☑	NV				☐				☐	☐	☑
Citalopram	Na		☐	NV	CD	↑	↕	☑		↑		☑	☑	☑
COLOXYL TABLE			☐	N	D			☐				☐	☐	☐
Metoprolol			☐	NV	CD	↑		☑				☑	☐	☑
Pantoprazole	(80 mg/day) B1, B12, Ca, Fe,		☑	NV	CD		↓	☑				☑	☐	☐
Rosuvastatin			☑	N	C			☑				☐	☐	☐
SENOKOT			☐		D			☐				☐	☐	☐

Transporter-mediated interactions and nutrients

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Organ (transporter)	Thiamine	Choline	Carnitine
Inhibitor function			
Liver	Citalopram (OCT1) Pantoprazole (OCT1)	Citalopram (OCT1) Pantoprazole (OCT1)	
Into kidneys	Citalopram (OCT2) Pantoprazole (OCT2)	Citalopram (OCT2) Pantoprazole (OCT2)	
Into muscles	Pantoprazole (OCT3)	Pantoprazole (OCT3)	Pantoprazole (OCT3)
Substrate function			
Into muscles	Citalopram (OCT3)	Citalopram (OCT3)	Citalopram (OCT3)

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

Biochemistry

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

Glycaemia

Currently prescribed 4 medications that alter glycaemia, being amlodipine, aspirin, citalopram, metoprolol and rosuvastatin.

Pharmaconutrition

Currently prescribed 6 medications that include nausea as a side effect.

Currently prescribed 5 medications that include vomiting, constipation and altered taste as side effects.

Currently prescribed 4 medications that include diarrhoea, dry mouth and sweating as side effects.

Currently prescribed 3 medications that include anaemia as a side effect.

Currently prescribed 2 medications that include altered availability of zinc, iron, vitamin C and riboflavin as side effects.

Amlodipine impairs zinc status.

Vitamin C (960 mg/day) attenuates aspirin-induced gastric injury.

Regular monitoring sodium levels recommended whilst citalopram prescribed.

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

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. Advisable to clarify magnesium status.

Statins interfere early in the cholesterol metabolic pathway and consequently decrease -

- conversion of sunlight-on-skin to vitamin D - vitamin D intervention recommended,

- production of CoQ10 - important in cellular energy production; CoQ10 intervention recommended,

- DHEA production - low DHEA associated with increased risk of metabolic syndrome; intervention recommended.

Advisable to clarify cholesterol status and ensure intervention is being effective, and that cholesterol levels are not too low.

Bowel management

Regular aperients prescribed,

Oral PRN aperient prescribed,

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mrs AGP’s appetite is quite variable and that if the doesn't like a meal she will preferentially eat a sandwich.

Observations

Mrs AGP is a pale, slender, pleasant lady whose sacral wounds were being dressed - she told me the food tastes awful - she was not convinced that it could be due to factors other than poor cooking!

Mrs AGP has lost weight further to a complicated hospitalisation - the consequences of which are likely contributing to slowing wound healing and poor appetite.

Pharmaconutrition assessment

Mrs AGP has been prescribed a proton pump inhibitor since admission ie one year ago and likely before then. 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.

Mrs AGP is in the difficult position of being prescribed a proton pump inhibitor and having a wound whereby the healing has slowed and is unlikely to heal properly whilst a proton pump inhibitor is prescribed. Advisable to 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 the proton pump inhibitor intervention can be ceased until the wound is healed.

Nutritional interventions that support to wound healing include -

- ensure adequate status of B12, magnesium, zinc and iron - a high dose of pantoprazole is prescribed which compromises their status,

- adequate vitamin D status - evidence indicates low vitamin D status is associated with delayed wound healing and currently prescribed rosuvastatin;

- adequate vitamin C - important in collagen formation and the strength of the collagen; both topical application and increased oral intake confer benefit. Currently prescribed pantoprazole which decreases availability of active vitamin C. It is likely wound healing will be delayed, and of poor quality whilst there is reduced availability of active vitamin C.

What else would you include?

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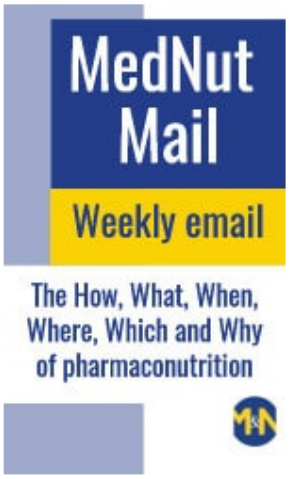

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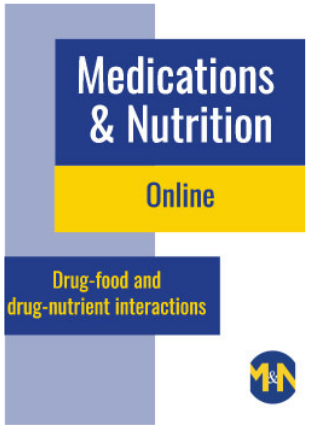

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