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

The daily double – metformin and proton pump inhibitors (PPI)

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Commentary

Both decease vitamin B12 absorption, and decrease thiamine availability.

Metformin is the fourth most commonly prescribed medicine in the world, and was discovered and developed in the late 1950's; the evidence that it negatively impacts vitamin B12 status has also been consistently published since the late 1950's. Even after 60 years of consistent evidence that metformin negatively impacts vitamin B12 status there is no recommendation in the Clinical Practice Guidelines for medical staff to regularly monitor B12 status once metformin is prescribed.

The PPIs decrease gastric acidity levels ie higher pH and therefore Intrinsic Factor (B12 transporter) is not released and so vitamin B12 is not transported to its site of absorption.

The evidence indicates the combination of metformin and a PPI has an additive negative impact on B12 levels.

Vitamin B12 is so important in so many different body functions such as production of myelin (the protective sheath surrounding neurons), astrocyte function (the intermediary between the blood vessels and the neurons), sense of touch, vision, balance, wound healing, pain management, continence control, and the list is much longer. Therefore, low B12 status can seriously negatively impact a person's quality of life.

Compounding the problem of B12 deficiency is the broad variability in pathology ranges for acceptable levels, especially the cut-off level for lower acceptable limit. Personal observation has noted that various lower cut-off levels range between 120, 180, 240 pmol/L both clinically (pathology lab ranges) and in the research papers. Some recent evidence based on neuro-imaging found that there was loss of memory once B12 levels are less than 200 pmol/L, and that interventions are successful.

As metformin can both inhibit most thiamine transporters and be transported by most thiamine transporters it is now deemed to be the universal probe for thiamine transporters.

Thiamine is typically absorbed during and after a meal and then transported to its relevant sites, whilst metformin is typically administered prior to a meal, fills the transporter slots and early evidence suggests thiamine is therefore unable to be transferred to its sites of action.

Both metformin and the PPI's have been found to inhibit the main thiamine transporters, being the Organic Cation Transporters (OCT) 1,2,3, whilst metformin has also been found to inhibit and be a substrate (can also be carried on that transporter) on other thiamine transporters such as THTR (Thiamine Transporter) and MATE (Multidrug And Toxic compound Extrusion).

The evidence indicates that drug-induced inhibition of thiamine transporters is likely to have a duration of about/at least an hour; the impact in the elderly has not been established and therefore it may be prudent to allow a longer duration of inhibition.

Thiamine is important in many different body functions such as energy metabolism and astrocyte function, hearing capacity, and more; in fact, astrocytes are very susceptible to thiamine status and lose function as thiamine becomes unavailable – poorly functioning astrocytes means damaged and dying neurons and therefore chronic neuropathic pain.

The PPIs can also indirectly inhibit thiamine availability as they decrease magnesium absorption – and magnesium is important in the activation of thiamine, vitamin D and iodine.

So, next time you see someone prescribed the daily double will you integrate the following into your clinical assessment?

- check their B12 status, and request it to be checked if it is not available,
- ascertain adequacy of thiamine intake,
- check that the thiamine intervention is not being administered at the same time as the metformin or PPI.

The daily double is a significant, common drug combination that can have a powerful negative impact on a person's quality of life, from impacting B12 levels with its negative effects especially on our neurological physiology, to impacting thiamine with its negative effects especially on both our neurological physiology and energy metabolism.

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: chronic pain, diverticulosis

Other: multiple myeloma, AF, hypercholesterolaemia, SODOE

Biochemistry with Pharmaconutritional Consequences

Na:	140	mmol/l	Hb:	116	g/L	Albumin:		g/L	BSL:		mmol/l
K:	4.1	mmol/l	Lymph:	0.9		Total Protein:		g/L	HbA1C:		
Urea:	4.6	mmol/l	MCV:	80	mmol/l	B12:	328	pmol/L	INR:		
Creatinine:	0.159	mmol/l	Zn:		umol/l	Folate:	16.0	nmol/L	TSH:		mIU/L

Other: eGFR 36, CRP 17, vit D 72, Fe 9, TRF 2.8, satn 13%, ferritin 92

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			☑				☐	☐	☐
Aspirin	C, Fe	☑		NV				☐				☐	☐	☑
BACTRIM	folate	☐		NV	D		↓	☐				☐	☐	☐
Calcium carbonate	Fe	☐			C			☐				☐	☐	☐
Cholecalciferol	(1000 iu/day)	☐						☐				☐	☐	☐
Dexamethasone	Ca, Cr, Iodine	☐					↑	☐				☐	☐	☑
DUODART	MR	☑		V	CD			☐				☐	☐	☐
FERROGRADUMET	Ca, Mg, Zn	☐		NV	CD			☐				☐	☐	☐
Frusemide	(20 mg/day) Ca, Cl, K, Mg, Na,	☑		NV	CD		↓	☐				☑	☐	☑
Hydromorphone	SR	☐		NV	CD		↓	☑				☑	☐	☐
Metoprolol		☐		NV	CD	↑		☑				☑	☐	☑
MOVICOL		☐		N	D			☐				☐	☐	☐
Pantoprazole	(40 mg/day) B1, B12, Ca, Fe,	☑		NV	CD		↓	☑				☑	☐	☐
Pregabalin		☐		NV	CD	↓	↑	☑		↑		☑	☑	☐
TARGIN		☐		NV	CD		↕	☑				☑	☑	☐
Thalidomide		☐		N	C		↑	☐				☑	☐	☐

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

Recent relevant available biochemistry indicates

- low Hb - associated with increased risk of falls, and poor appetite; ? pantoprazole impact. Given Ferrograd+C is in a matrix it has an extended period until dissolution, especially in the presence of pantoprazole therefore advisable to consider an alternative, more effective intervention.
- marginally adequate B12 – likely indicates pantoprazole impact on absorption

Advisable to check plasma proteins (albumin, total proteins) as markers of nutritional status. The plasma proteins are the primary transporters for four of the prescribed drugs and hypoproteinaemia may alter their effects.

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

Advisable to monitor folate levels whilst bactrim prescribed.

Glucocorticoid dose and duration associated with lower vitamin D levels; vitamin D enhances the anti-inflammatory effects of glucocorticoids.

Frusemide increases urinary excretion of calcium, magnesium, potassium, sodium and thiamine.

Pantoprazole decreases B12, vitamin C, magnesium, zinc and iron absorption, may decrease calcium absorption, and decreases availability of thiamine through inhibition of some of its transporters.

Currently prescribed the daily double ie two drugs decrease magnesium availability - being frusemide and pantoprazole. 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 remains unknown whilst magnesium levels within acceptable range however if magnesium levels are low then that typically indicates significant cellular depletion and intervention recommended. Advisable to check magnesium status and ensure > 0.80 units (currently recommended acceptable lower limit)

Impacts on thiamine transporters

- **THTR2** (thiamine transporter 2) - facilitates absorption from the intestine into the enterocytes and retinal cells, and crosses the blood-brain barrier; bactrim is both an inhibitor (blocks transport function) and a substrate (can be carried by the transporter);

- **OCT1** – facilities liver uptake of thiamine; pantoprazole is an inhibitor;
- **OCT2** – facilitates kidney uptake of thiamine; bactrim, metoprolol and pantoprazole are inhibitors; and bactrim is also a substrate;
- **OCT3** – facilitates skeletal muscle uptake; pantoprazole is an inhibitor; bactrim is a substrate.

Given the combination of drugs directly thiamine availability plus the daily double negatively impacting magnesium status, advisable to monitor thiamine status; if an intervention is considered then administer at a time that Bactrim, metoprolol and pantoprazole are not administered.

Mr AAH is a pale, unwell-looking, charming big-framed man of size who was lying on his bed reading a book when I went to speak to him. Mr AAH told me he had been a jogger and big eater until the mid nineties when he developed leg problems which took 10 years to resolve - during that time he gained weight. Mr AAH told me he sometimes feels like vomiting due to pain, and that food does not have as much taste these days.

Mr AAH has returned from hospital with a wound and infection. Nutritional interventions that support to wound healing include

- adequate B12 - pantoprazole is prescribed which compromises their absorption and availability
- adequate magnesium, zinc and iron – the daily double is prescribed which compromises their absorption and availability
- adequate vitamin C - important in collagen formation and the strength of the collagen. Pantoprazole reduces 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. It is also likely vitamin C interventions are unlikely to be effective whilst a proton pump inhibitor is prescribed.

Mr AAH is in the difficult position of being prescribed a proton pump inhibitor and having a wound that 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.

Mr AAH ‘s diagnoses include chronic pain - nutritional factors that may be useful to consider in pain management include

- vitamin C - pain increases the reactive substances (formerly Reactive Oxygen Species) within cells. Vitamin C is important in quenching reactive substances and if there is insufficient vitamin C then cell status becomes compromised and the cells typically die which also causes pain. Advisable to consider a vitamin C intervention - the optimal intervention is 500 mg vitamin C/day (if more than 500 mg vitamin C administered at a time then the excess above 500 mg is not absorbed as the vitamin C transporters are overloaded). Vitamin C is not considered part of the pain management armament however it won't cause harm and evidence suggests it may confer benefit. It is unlikely vitamin C interventions will be effective whilst pantoprazole is prescribed.
- low B12 exacerbates elevated TNF- α which is an inflammatory response marker; elevation of the inflammatory response can include a pain response and currently prescribed pantoprazole therefore advisable to monitor B12 status. There is disagreement between pathology ranges and research findings with regard to appropriate B12 levels - recent neuro-imaging research shows a direct causal link between B12 status and reduced memory, and recommend B12 interventions once levels are less than 300 pmol/L.
- magnesium – proposed mechanism magnesium blocks the NMDA receptor channels in the spinal cord and thus limits the influx of calcium ie reduces the risk of excitotoxicity and consequent exacerbation of pain; currently prescribed the daily double therefore advisable to check magnesium levels.

Zinc has many functions in the body including being important in the sense of taste. Frusemide increases zinc excretion, and there is increasing evidence that proton pump inhibitors such as pantoprazole significantly impair zinc status. Advisable to check zinc levels and if low then consider a short term (90-120 days) zinc intervention however its effectiveness is questionable given the daily double is prescribed.

Mr AAH's combination of prescribed medicines are impacting a range of nutrients that directly impact his quality of life - with zinc being of particular note as tasty food is one of his few remaining pleasures.

What else would you include?

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