MedNut Mail

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

Metformin and thiamine

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Editorial

Membrane transporters are steadily gaining recognition as important factors in the absorption, distribution, metabolism, and excretion of many nutrients, as well as many xenobiotic compounds such as prescribed medicines, toxic metals, many agricultural chemicals.

The combination of polypharmacy and the current regulatory requirements, necessitate all new drugs be evaluated for their impact on a predetermined range of transporters, and their proposed mechanisms of action ie as substrates or inhibitors. Metformin is the universal probe for evaluating potential thiamine transporter-mediated drug-drug interactions as it functions as both a substrate and an inhibitor.

Metformin is the fourth mostly commonly prescribed medicine globally, consequently its side effects such as negative impacts on various nutrients, affect a significant percentage of the global population – certainly many millions of people.

Metformin improves insulin resistance by increasing glucose uptake into muscle and adipose tissue and by decreasing liver-based gluconeogenesis.

Thiamine cannot be produced in the body and therefore must be obtained via intestinal absorption from exogenous sources such as food and gut microbiota production. Thiamine's availability is determined by adequacy of intake, magnesium availability, and degree of xenobiotic interference.

Thiamine is essential for metabolism to proceed, and functions by regulating molecular oxygen homeostasis and mitochondrial ATP production. Functions include carbohydrate metabolism ie generating energy, glucose metabolism, being a cofactor for ATP production (primary source of energy for cells), production of neurotransmitters, lipid metabolism, amino acid modification, and neuromodulation.

Thiamine deficiency causes regionally selective neuronal death, mitochondrial dysfunction, energy shortage, chronic oxidative stress, altered mental status (confusion, lethargy and apathy), altered oculomotor dysfunction (involuntary rhythmic and/or unco-ordinated eye movements), altered ataxia of stance and gait (ranging from mild imbalance and unsteadiness to wide-based shuffling to inability to sit or stand). Astrocytes are among the first cells to be affected by thiamine deficiency in advance of neuronal cell death (MedNut Mail 2022-06-29 - https://medicationsandnutrition.online/astrocytes-and-pharmaconutrition/).

Thiamine deficiency manifests as nausea, vomiting, constipation, loss of appetite, altered swallow capability, abdominal discomfort, depression, fatigue, confusion, disturbed sleep, irritability, agitation, lethargy – this combination is so common, especially in the elderly, as to not be useful for identifying thiamine deficiency specifically.

Key thiamine transporters include -

- THTR1 - from gut to epithelia, skeletal muscle, nervous system, eye, placenta, kidney,
- THTR2 – from gut to epithelia, adipose tissue, breast tissue, liver, lymphocytes, spleen, gallbladder, placenta, pancreas, brain,
- OCT1 - blood to liver,
- OCT2 - blood to kidney,
- OCT3 - blood to muscles,
- MATE1/2 - kidney to urine,
- assorted others.

Blood tests for thiamine status are unlikely to be reliable as thiamine transport is inhibited and consequently thiamine can neither enter nor exit relevant organs and cells. There is evidence that some drugs inhibit transporters for 6 hours however I have been unable to ascertain metformin's duration of inhibition. Therefore, management strategies to consider would include –

- checking thiamine status and ascertaining whether blood levels are acceptable or high – and then clarifying whether any prescribed medications are inhibiting any relevant transporters;
- determining duration of metformin prescription. If it is 6+ months then perhaps a regular thiamine intervention be considered and administered at a different time from metformin. For example, if metformin is administered at 08:00 and 16:00 (Aged Care hours) then thiamine intervention could be administered at lunchtime (thiamine can also inhibit its transporters);
- if lethargy and/or drowsiness is interfering with food intake then suggest a thiamine and magnesium intervention and administered at a different time from metformin.

What actions will you initiate when metformin is one of the prescribed medications, will you –

- clarify thiamine status and then recommend a thiamine intervention and try and identify a suitable time for its administration?

- clarify magnesium status and then recommend a magnesium intervention and try and identify a suitable time for its administration?
- try and ascertain thiamine status based on expressed signs and symptoms?

Conclusions

Transporter-mediated drug-nutrient interactions are adding an extra layer of complexity to managing drug-nutrient interactions. Given thiamine's importance are we already seeing the lack of thiamine availability being expressed but not 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:

Other: CRF, hypercholesterolaemia, pain

Biochemistry with Pharmaconutritional Consequences

Na:	140	mmol/l	Hb:	111	g/L	Albumin:	36	g/L	BSL:		mmol/l
K:	4.9	mmol/l	Lymph:	1.9		Total Protein:	75	g/L	HbA1C:		
Urea:	9.1	mmol/l	MCV:	96	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.123	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR 45, ESR 97, CRP 30

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
Alendronate sodiu	Ca	☐	NV	CD	↑		☑				☐	☑	☐
CALTRATE	Fe	☐		C			☐				☐	☐	☐
Cholecalciferol	(1/day)	☐					☐				☐	☐	☐
Lactulose		☐	NV	D		↓	☐				☐	☐	☑
LASIX	(20 mg/day) Ca, Cl, K, Mg, Na,	☑	NV	CD		↓	☐				☑	☐	☑
LIPITOR		☑	NV	CD	↑	↓	☑				☐	☐	☐
MOVICOL		☐	N	D			☐				☐	☐	☐
PANADOL OSTEO		☐	NV	CD			☐				☐	☐	☐
Perindopril		☐	NV	D			☑				☑	☐	☐
PRISTIQ	Na	☐	NV	CD	↕	↓	☑				☐	☐	☐
SOMAC	(40 mg/day) B1, B12, Ca, Fe,	☑	NV	CD		↓	☑				☑	☐	☐
TARGIN		☐	NV	CD		↕	☑				☑	☑	☐

Summary of medications, nutrients and transporters

Organ·(transporter)¤	Thiamine¤	Choline¤	Carnitine¤
Inhibitor·function¤	¤	¤	¤
Liver·¤	Somac·(OCT1)¤	Somac·(OCT1)¤	¤
Into·kidneys·¤	Somac·(OCT2)¶ Naloxone·part·of·Targin·(OCT2)¤	Somac·(OCT2)¶ Naloxone·part·of·Targin·(OCT2)¤	¤
Into·muscles¤	Somac·(OCT3)¤	Somac·(OCT3)¤	Somac·(OCT3)¤

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

Data summary

Biochemistry

Relevant biochemistry mostly within acceptable ranges however B12 status is marginal and likely high risk of ongoing depletion due to Nexium prescription.

Glycaemia

Currently prescribed 1 medication that alters glycaemia, being aspirin.

Pharmaconutrition

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

Chronic use of coloxyl + senna may promote excessive loss of water and electrolytes, especially potassium, and their regular monitoring recommended.

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

Calcium carbonate requires gastric acidity for absorption however Nexium prescribed therefore advisable to consider calcium citrate which does not require gastric acidity for absorption.

Bowel management

Regular aperients prescribed

Oral + anal PRN interventions prescribed

No Nurse Initiated interventions administered

Staff comments

Staff advise Mrs AGK eats well, that she sleeps until about 10:00 am is showered and has breakfast. Staff also commented Mrs AGK has frequent chest infections and has recently ceased (yet another) course of antibiotics.

Observations

Mrs AGK is a small, pale, frail lady with cold hands and who was lying in bed when I went to speak to her - she responded to my presence but not my questions.

Currently weight stable.

Pharmaconutrition assessment

Since Mrs AGK is pale, advisable to check iron levels especially since Nexium is prescribed as it is associated with decreased iron absorption.

Mrs AGK is reported to have frequent chest infections which are treated with antibiotics. Frequent infections decrease the immune system especially zinc status. Zinc is important in a range of body functions, including sense of taste and release of the hunger hormone Neuropeptide Y. Advisable to check zinc levels especially since Nexium is prescribed as it is associated with decreased zinc absorption.

Mrs AGK has been prescribed a proton pump inhibitor for more than 4 years. There is increasing evidence that long-term (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 consider 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).

Mrs AGK's diagnoses include arthritis which is a cause of 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 - Vitamin C is not considered part of the pain management armament however it won't cause harm and evidence suggests it may confer benefit. Currently prescribed Nexium which decreases conversion of vitamin C to its active form.

- 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 Nexium therefore advisable to check B12 status.

- 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 Nexium which decreases magnesium absorption.

Mrs AGK's diagnoses include falls - nutritional factors to consider in falls management include -

- low calcium - more likely to be low if potassium or magnesium low; important in muscle function, currently prescribed Nexium therefore advisable to clarify status;

- low B12 - is important in the righting reflex when a person stumbles; prescribed Nexium therefore advisable to check status;

- low zinc – can decrease food intake through altered sense of taste and poor appetite, and consequently reduced muscle mass; currently prescribed Nexium therefore advisable to check status;

- low magnesium - magnesium is important in vitamin D activation and muscle function, amongst other functions. Also currently prescribed Nexium which significantly decreases magnesium absorption. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status Advisable to clarify magnesium status.

Mrs AGK's diagnoses include deafness - nutritional factors that may be useful to consider in deafness management include -

- B12 and/or folate - associated with deafness; currently prescribed Nexium therefore advisable to check B12 status and if low then intervention recommended;
- vitamin C - inadequate dietary intake associated with deafness; currently prescribed Nexium which reduces conversion of vitamin C to its active form;

- zinc - inadequate zinc status has been associated with impaired hearing; currently prescribed Nexium therefore advisable to check zinc status and if low then intervention recommended;
- thiamine – associated with bilateral hearing loss and proposed mechanism of action is that thiamine transporter OCT2 is expressed in the hair cells of the cochlea therefore interruptions to thiamine accessibility are likely to impact hair cell function; currently prescribed Nexium which decreases thiamine availability both directly and indirectly.

What else would you include?

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