MedNut Mail

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

Levodopa +carbidopa and thiamine

Y Coleman

10th April 2024

https://medicationsandnutrition.online/mednutmail/

Editorial

Levodopa + carbidopa and thiamine encompass a range of interactions that have significant consequences to Parkinson's Disease (PD) progression.

The majority of people diagnosed with PD are treated with medications to relieve the symptoms of the disease. The medications fall into 2 primary groups, being –

- levodopa-based which stimulate the remaining cells in the substantia nigra to produce more dopamine;
- anticholinergic-based which inhibit some of the acetylcholine in order to restore the dopamine-acetylcholine balance in the brain.

The current general consensus is that PD is caused by a dopamine deficiency. Some researchers are now questioning whether dopamine deficiency is a cause of PD or a consequence of other metabolic events. Recent evidence suggests PD may be due to a focal deficiency of thiamine in the brain. Causes of the focal deficiency include either dysfunction of an intracellular thiamine transporter or structural enzymatic abnormalities.

Inadequate thiamine has been found to decrease the concentration of dopamine in the striatum. Intra-striatal administration of thiamine triphosphate has been found to induce dopamine release.

Thiamine is essential in molecular oxygen homeostasis and mitochondrial ATP production ie the basis of the body's metabolism. Inadequate thiamine availability alters mitochondrial function with resultant reduced, less-efficient energy production. A consequent cascade of responses includes vascular reactivity, inflammation, cell apoptosis, and organ dysfunction/failure.

Direct interaction

The evidence from randomized controlled trial sand other intervention studies for direct interactions between levodopa + carbidopa and thiamine is limited.

Indirect interactions

There are some key points whereby thiamine availability could compromise or be compromised.

1. Dopamine deficiency

Some authors suggest dopamine deficiency is likely due to interference with thiamine status at either the conversion of -

- tyrosine to dopamine by tyrosine hydroxylase; or
- phenylalanine to tyrosine.

Inadequate thiamine availability is the proposed mechanism of interference in these key operations however the evidence is difficult to locate.

Dopamine is a substrate for thiamine membrane transporters OCT2 and OCT3. Physiological and/or therapeutic and/or environmental inhibitors of these transporters are likely to limit dopamine availability.

2. Transporter - OCT1

OCT1 is a significant thiamine transporter. Very limited evidence indicates levodopa might be transported by OCT1 to a small extent, and not very efficiently. If levodopa is a substrate, then it has the potential to displace thiamine uptake.

3. Magnesium

Concurrent administration of magnesium oxide (MgO) with levodopa + carbidopa decreases their (drug) absorption and availability. Vitamin C dose-dependently decreases the negative impact of MgO on levodopa + carbidopa. It seems likely other forms of magnesium may have a similar effect. (Refer MedNut Levodopa, magnesium and vitamin C).

4. Hyperglycaemia (excessive glucose availability)

Thiamine Transporters 1/2 (THTR1/2) are integral to thiamine transport and uptake throughout the body. Hyperglycaemia induces downregulation of THTR1/2.

Protein phosphatase 2A (PP2A) is the main phosphatase responsible for regulating tyrosine hydroxylase activity. Hyperglycaemia-induced activation of PP2A contributes to an inflammatory response, and probable endothelial cell death. Thiamine intervention, as benfotiamine, inhibited the hyperglycaemic activation of PP2A and cell death.

High-dose thiamine interventions have been found to reduce or reverse hyperglycaemia-related activation effects and result in significantly improved glucose tolerance. Seemingly the levodopa + carbidopa-induced hyperglycaemia increases the demand for thiamine in order for glucose tolerance to be maintained.

Carriers

Both levodopa and thiamine are carried by albumin, however they occupy different sites from each other ie no competitive binding.

Comment

Given the commonality of PD (second most common neurological nasty globally), the importance of thiamine in neurological function, and the consistency of positive responses to thiamine interventions, the lack of evidence in relation to interactions between levodopa + carbidopa and thiamine is both remarkable and alarming.

Clinical considerations

Case study evidence implies levodopa + carbidopa-induced hyperglycaemia increases the requirement for thiamine.

The timeframe from dose administration to onset of hyperglycaemia and duration of hyperglycaemia would be useful information for both -

- inclusion in the Product Information documents, and

- clinical management strategies for hyperglycaemia.

Clinical questions

What actions will you initiate as you a review a person whose prescribed medications include levodopa + carbidopa, will you -

- recommend regular monitoring of thiamine and magnesium levels?
- consider the negative impacts of other prescribed medications on thiamine and magnesium status?
- recommend prophylactic thiamine interventions as a management strategy for hyperglycaemia-induced increases thiamine requirements?
- recommend the Medications Advisory Committee develop guidelines for thiamine administration when levodopa + carbidopa is prescribed?

Conclusions

The levodopa + carbidopa and thiamine interactions are likely to be indirect, with hyperglycaemia-induced consequences being a significant contributor.

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: vit D def

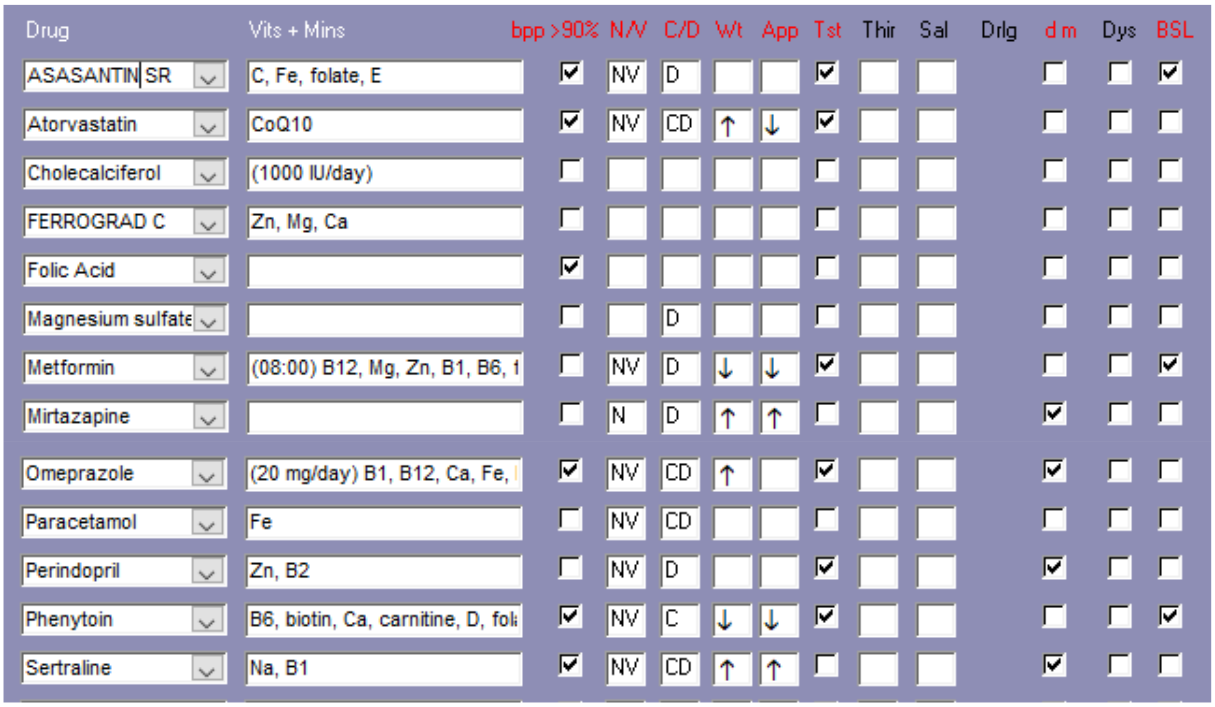
Other: epilepsy, Ca oesophagus + cervix, ETOH abuse

Biochemistry with Pharmaconutrition Consequences

Na:	139	mmol/l	Hb:	154	g/L	Albumin:	33	g/L	BSL:		mmol/l
K:	3.9	mmol/l	Lymph:	1.3		Total Protein:	62	g/L	HbA1C:	6.0	
Urea:	5.8	mmol/l	MCV:	98	mmol/l	B12:	112	pmol/L	INR:		
Creatinine:	0.051	mmol/l	Zn:		umol/l	Folate:	34.2	nmol/L	TSH:	1.85	mIU/L

Other: hos 1.07, Mg 0.66, CRP 34, chol 4.1, Tg 3.8, HDL 0.94, LDL 1.4, LDL:HDL 1.5, chol:HDL 4.4, vit D 89, active B12 24, F

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
ASASANTIN SR	C, Fe, folate, E	☑		NV	D			☑				☐	☐	☑
Atorvastatin	CoQ10	☑		NV	CD	↑	↓	☑				☐	☐	☐
Cholecalciferol	(1000 IU/day)	☐						☐				☐	☐	☐
FERROGRAD C	Zn, Mg, Ca	☐						☐				☐	☐	☐
Folic Acid		☑						☐				☐	☐	☐
Magnesium sulfate		☐			D			☐				☐	☐	☐
Metformin	(08:00) B12, Mg, Zn, B1, B6, f	☐		NV	D	↓	↓	☑				☐	☐	☑
Mirtazapine		☐		N	D	↑	↑	☐				☑	☐	☐
Omeprazole	(20 mg/day) B1, B12, Ca, Fe,	☑		NV	CD	↑		☑				☑	☐	☐
Paracetamol	Fe	☐		NV	CD			☐				☐	☐	☐
Perindopril	Zn, B2	☐		NV	D			☑				☑	☐	☐
Phenytoin	B6, biotin, Ca, carnitine, D, fol	☑		NV	C	↓	↓	☑				☐	☐	☑
Sertraline	Na, B1	☑		NV	CD	↑	↑	☐				☑	☐	☐

Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OCT3		THTR2		OCTN1		MATE1		MATE2		OAT1	
Nutrients - Substrates	B1, choline		B1, choline		B1, choline, carnitine		B1, B6		Carnitine, choline		B1		B1		B9, B5, pyridoxic acid (B6), B7	
Nutrients - Inh									vit D, choline							
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Asasantin																Y
metformin	Y	Y	Y		Y		Y	Y	Y		Y		Y			
Mirtazapine				Y												
omeprazole		Y		Y		Y										
Paracetamol																Y
Sertraline		Y		Y	Y			Y								

Sub – substrate, Inh – inhibitor, B1 – thiamine, B2 – riboflavin, B3 – niacin, B5 – pantothenic acid, B6 – pyridoxine, B7 – biotin, B9 – folic acid, B12 – cobalamin, NMN – N-methylnicotinamide

Comments – medication and nutrition impacts only

Data summary

Biochemistry

Recent relevant available biochemistry indicates –
- low albumin – a key transporter of both endogenous and exogenous substances in the blood, consequently low levels can alter drug effects;
- elevated low B12 – currently prescribed metformin and omeprazole therefore intervention recommended;
- low magnesium - commenced intervention 4 months ago that does not seem to be effective as current Mg levels still very low – likely negatively impacted by currently prescribed ferrograd C, metformin and omeprazole. Advisable to review current magnesium intervention.
- marginal vit D - current intervention 1000 IU/day. Currently prescribed metformin and atorvastatin both of which negatively impact vitamin D levels. Advisable to monitor status on a regular basis.

Glycaemia

BSLs
- before breakfast -6.91-7.7; recommended range 4-6;
- tested weekly;
- reportable limits: < 4 and > 20;
- last HbA1c indicates good glycaemic control.

Diabetes drugs
- metformin has a duration of 12 hours.

Diabetes drugs coverage
- before breakfast BSLs - minimal, if any, coverage from previous morning's dose;
- before evening meal BSLs - covered by current morning's dose.

Currently prescribed 8 medications that alter glycaemia.

Pharmaconutrition

Currently prescribed 9 medications that include nausea and vomiting as side effects.

Currently prescribed 8 medications that include diarrhoea as a side effect.

Currently prescribed 7 medications that include constipation and altered taste as

side effects.

Currently prescribed 6 medications that include weight changes as a side effect.

Currently prescribed 5 medications that include appetite changes as a side effect.

Currently prescribed 4 medications that include anaemia, altered potassium and zinc levels, dry mouth and sweating as side effects.

Currently prescribed 3 medications that include hyponatraemia, altered thiamine, folate, calcium, magnesium and iron levels, and tremor as side effects.

Aspirin inhibits vitamin C absorption by inhibiting access to albumin for transport, and folic acid (mechanism currently unknown). Advisable to administer vitamin C prior to aspirin to minimise aspirin's negative impact on vitamin C absorption. Advisable for aspirin and magnesium to be administered at different times from each other as magnesium inhibits aspirin effect.
Vitamin C (960 mg/day) attenuates aspirin-induced gastric injury.

Coffee inhibits vitamin D uptake by osteoblasts (bone builders) by inhibiting their vitamin D receptors, and consequently decreases calcium and zinc absorption.

Ferrograd+C comprises ferrous sulfate + vitamin C. Iron is available in two forms being ferrous and ferric - ferrous is the absorbable form whilst ferric requires vitamin C to convert it to ferrous in order to be absorbed. The combination of iron in a ferrous form plus vitamin C is unnecessary and implies the drug company is being disingenuous. Ferrograd+C has a very slow rate of dissolution and poor rate of absorption ie less than 30%. Ferrous sulfate has a rapid rate of dissolution and rate of absorption of 40+% whilst ferrous fumarate also has a rapid rate of dissolution and rate of absorption of 30+%. Advisable to review iron intervention and consider alternative options.

Ferrous sulfate component decreases zinc absorption.

Megafol has been prescribed for 10 years - evidence indicates excessive folic acid intake diminishes cognitive function. Folic acid levels were recently checked and are high however prescribed 4 medicines that decrease folic acid availability therefore advisable to either have a "folic acid holiday" for a defined period or review current dose and consider a lower dose.

Metformin decreases B12, Mg, Zn, B1, B6, vit D, folate absorption and there is now a

recommendation for regular monitoring of B12 status ie at least annually.

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

Dietary levels of caffeine intake in conjunction with paracetamol inhibit antinocieception.

Concurrent ingestion of paracetamol and iron resulted in increased rate of iron absorption and decreased extent of drug absorption; the authors advise drug and iron to be administered at different times from each other.

Perindopril impairs zinc status.

Phenytoin decreases biotin and carnitine absorption and decreases availability of folic acid and vitamin D.

Regular monitoring sodium levels recommended whilst sertraline and mirtazepine prescribed.

The evidence is increasing that proton pump inhibitors 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 remains unknown whilst magnesium levels within acceptable range however if magnesium levels are low then that typically indicates significant cellular depletion. Currently prescribed ferrograd C, metformin and omeprazole which all decrease magnesium availability. Women require 320 mg elemental magnesium per day, magnesium supplements such as mag-sup typically provide 37.4 mg elemental magnesium per tab. Advisable to effectiveness of current intervention.

Statins interfere early in the cholesterol metabolic pathway and consequently decrease -
- conversion of sun 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.

Currently prescribed two drugs that decrease B12 absorption being metformin and

omeprazole - recent evidence indicates an additive negative effect on B12 status. Current status low therefore advisable to consider an intervention.

Staff comments

Staff advise Mrs ACX eats well, and seems to be eating more vegetables.

Observations

Mrs ACX is a pale, charming, sensible lady who was lying in her bed when I went to speak to her - she told me her sense of taste is changing and that she finds she prefers to eat yoghurts and more vegetables.

Mrs ACX has remained weight stable for the last 6 months.

Pharmaconutrition comments

Mrs ACX's glycaemia is tested in the mornings on a weekly basis - advisable to check afternoon glycaemia for 3 days and clarify status.

Mrs ACX has been prescribed a proton pump inhibitor for at least 12 years, and probably 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.

Consequently, advisable to reconsider reviewing current proton pump inhibitor prescription and consider -
- whether proton pump inhibitor prescription is still required, or
- 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 ACX's diagnoses include chronic pain - nutritional factors that may be useful to consider in pain management include -

- vitamin D - evidence indicates increasingly brittle pain control with decreasing/low vitamin D levels. Advisable to monitor vitamin D levels;
- 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. Whilst not considered part of the pain management armament, Vitamin C it won't cause harm and evidence suggests it may confer benefit. Currently prescribed omeprazole which decreases conversion of vitamin C to its active form and aspirin which inhibits vitamin C transport in the blood;
- 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 metformin and omeprazole therefore advisable to monitor B12 status and initiate an intervention as required;
- 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 ferrograd C, metformin and omeprazole which all decrease magnesium availability and a low dose magnesium intervention. Advisable to monitor status and ensure intervention is being effective.

Low B12 associated with increased TNF-α response and demyelination; TNF-α is a key marker of the inflammatory response. B12 deficiency manifests as weakness, light-headedness, vertigo, tinnitus, palpitations, angina, sore tongue, anorexia, moderate weight loss, diarrhoea, demyelination, axonal degeneration, parasthesias, unsteady gait, limb stiffness and weakness, irritability, apathy, somnolence, emotional instability, marked confusional or depressive states; visual impairment. Currently prescribed metformin and omeprazole therefore advisable to consider a B12 intervention as levels are low.

Mrs ACX's diagnoses include falls - nutritional factors that may be useful to ensure within acceptable ranges include –

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

- vitamin D – increasing vitamin D intake increases muscle strength and decreases falls; currently prescribed colecalciferol therefore advisable to monitor vitamin D status;
- B12 - is important in the righting reflex when a person stumbles; prescribed metformin and omeprazole therefore advisable to monitor status;
- zinc – can decrease food intake through altered sense of taste and poor appetite, and consequently reduced muscle mass; currently prescribed metformin and omeprazole therefore advisable to monitor status;
- magnesium - magnesium is important in vitamin D activation, de novo carnitine production, and muscle function, amongst other functions. Also currently prescribed ferrograd C, metformin and omeprazole which significantly decrease magnesium availability. Magnesium is low and prescribed a low-dose intervention - advisable to monitor magnesium status and ensure the intervention is being effective;
- thiamine –is important in balance and position sense. Currently prescribed metformin, omeprazole and sertraline therefore advisable to monitor status;
- carnitine - carnitine is both absorbed and produced de novo, and is important in a range of muscle functions. Omeprazole inhibits OCT3 which transports carnitine therefore advisable to clarify status.

There are a number of nutritional interventions to improve insulin sensitivity or reduce insulin resistance including

- vitamin D within acceptable range - early evidence indicates low vitamin D is a predictor of peripheral insulin resistance and elevated inflammatory response markers. Currently prescribed metformin, atorvastatin and phenytoin as well as a colecalciferol supplement therefore advisable to monitor status;
- magnesium – is important in glycaemic control and inadequate intake may impair insulin synthesis, secretion and signalling pathways; in fact there is evidence of an inverse correlation between magnesium status and diabetes incidence. Currently prescribed ferrograd C, metformin and omeprazole which significantly decreases magnesium absorption, and a magnesium intervention. Advisable to monitor status and ensure intervention is being effective;
- thiamine - people with diabetes have a significantly increased urinary excretion of thiamine; thiamine is important in glycaemic control; currently also prescribed metformin, omeprazole and sertraline which further decreases thiamine availability excretion;
- biotin – evidence indicates biotin is important in a number of steps in carbohydrate metabolism; currently prescribed phenytoin, asasantin and paracetamol which significantly negatively impacts biotin availability;

- zinc – is integral to insulin formation, and enhances insulin sensitivity through stimulation of insulin receptors; inadequate intake may impair insulin synthesis, secretion and signalling pathways. It is important in the glucose metabolism, protects the mitochondria from oxidative stress and glycation, and altered glomerular function, as well as modifying the inflammatory response pathway and activation of the polyol pathway (a part of intracellular signalling and metabolism). Currently prescribed metformin and omeprazole therefore advisable to monitor status;
- potassium - important in the glucose metabolism, and functions in β-cells; inadequate intake may impair insulin synthesis, secretion and signalling pathways. Currently prescribed omeprazole therefore advisable to monitor status;
- calcium - important in the glucose metabolism, and functions in β-cells; inadequate intake may impair insulin synthesis, secretion and signalling pathways and prescribed omeprazole therefore advisable to monitor status.

What else would you include?

Please read this as it is important …

The information in this article is provided to support Health Professionals. It is not an exhaustive protocol and Health Professionals are advised that adequate professional supervision is accessed to ensure that Duty of Care obligations with respect to safe administration of medicines is met for each consumer.

Medications have profoundly and positively changed health outcomes however they do generally come with some nutritional harms. By identifying and addressing the nutritional harms, optimal health outcomes are closer to being achieved.

You may be interested in some of our other products …

MedNut Mail is our free weekly email that identifies and comments upon some aspect of pharmaconutrition.

For more information click here.

For innovative clinicians wanting to include drug-nutrition interactions into their daily clinical practice in order to optimise outcomes for those in their care.

Subscriptions start from AU$29.95

For more information click here.