MedNut Mail

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

Levodopa +carbidopa, magnesium and vitamin C

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Editorial

The levodopa + carbidopa, magnesium and vitamin C interaction has only recently gained recognition. Levodopa is commonly prescribed for those diagnosed with Parkinson's Disease. Carbidopa's primary function is to minimise B6's impairment of levodopa absorption.

Recent evidence (https://doi.org/10.1016/j.prdoa.2023.100227) indicates concurrent administration of magnesium oxide (MgO) with levodopa + carbidopa decreases their absorption and availability. The proposed mechanisms of action for MgO's effect include -

- altering pH - both levodopa and carbidopa are pH sensitive and their levels decrease as pH increases from acid to neutral; and
- directly interacting with these drugs.

Vitamin C decreases the negative impact of magnesium oxide on levodopa + carbidopa (https://doi.org/10.1002/brb3.2672) with the response being dose-dependent. The study included 2 vitamin C test doses, being 200 mg and 500 mg. The 500 mg test dose minimised the MgO effect to the same level as MgO not being administered.

An earlier study found that vitamin C improved levodopa absorption with the proposed mechanisms of action being -

- a direct vitamin C antioxidant effect on levodopa;
- vitamin C preventing MgO-induced carbidopa breakdown. Maintenance of carbidopa levels means less vitamin B6 being available to decrease levodopa absorption.

Clinical Considerations

If a vitamin C intervention is to be considered when levodopa + carbidopa is prescribed, then when would be the best time to administer it? Should the vitamin C be administered prior to levodopa + carbidopa to ensure an adequate availability of vitamin C as the drug is absorbed? Or could they all be administered at a similar time, especially since it is unlikely there will be competition for transporters?

What would be a useful vitamin C intervention to consider? The combination of greater conferred benefit and SVCT1 (sodium vitamin C transporter) carrying capacity indicates 500 mg vitamin C doses to be an acceptable level of intervention.

Whilst the evidence is based on MgO, it is likely other magnesium formulations will similarly interact with levodopa + carbidopa medications, and so it is also likely vitamin C interventions will confer similar levels of benefit.

Clinical Questions

What actions will you initiate as you a review a person's prescribed medications that include levodopa + carbidopa and magnesium, will you –

- recommend a vitamin C intervention, and at what dose and times?
- recommend a review of magnesium's administration time in relation to levodopa + carbidopa administration?
- recommend the Medications Advisory Committee develop guidelines for the administration of vitamin C when magnesium is prescribed in conjunction with levodopa + carbidopa?

Conclusions

The levodopa + carbidopa, magnesium and vitamin C interaction has significant implications for those with Parkinsons Disease. Concurrent administration of vitamin C has been found to modify the negative impacts of magnesium on the therapeutic effects of levodopa + carbidopa.

Disclaimer

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.

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: cholecystectomy, DEAFNESS, lower leg oedema, IDC

Other: GORD, hyperlipidaemia, pain, anxiety, BLINDNESS

Biochemistry with Pharmaconutrition Consequences

Na:	140	mmol/l	Hb:	113	g/L	Albumin:		g/L	BSL:		mmol/l
K:	3.9	mmol/l	Lymph:	2.7		Total Protein:		g/L	HbA1C:	8.1	
Urea:	6.2	mmol/l	MCV:	90	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.092	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR > 60

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
COLOXYL WITH S		☐		D			☐				☐	☐	☐
Metformin	08:00 B12, Mg, Zn, B1, B6, B9	☐	NV	D	↓	↓	☑				☐	☐	☑
Omeprazole	(20 mg/day) B1, B12, Ca, Fe,	☑	NV	CD	↑		☑				☑	☐	☐
Sertraline	Na, B1	☑	NV	CD	↑	↑	☐				☑	☐	☐
Simvastatin	E, CoQ10	☑	NV	CD			☑				☐	☐	☐
		▩					▩				▩	▩	▩

Extra drug: novomix 30 nocte

Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OCT3		THTR2		OCTN1		MATE1		MATE2		OAT1	
Nutrients - Substrates	B1, choline, carnitine		B1, choline, NMN, carnitine		B1		B1, B6		carnitine		B1, NMN		B1, NMN		B9, B5, B6	
Nutrients - Inh																
DRUG	Sub	Inh	Sub	Inh	Sub	Inh	Sub	Inh	Sub	Inh	Sub	Inh	Sub	Inh	Sub	Inh
Metformin	Y	Y	Y		Y		Y	Y	Y		Y		Y			
Omeprazole		Y		Y		Y										
Sertraline		Y		Y	Y			Y								
Simvastatin																Y
Omeprazole inhibits BCRP; Simvastatin inhibits OAT3; is a P-gp substrate																
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 "old" biochemistry indicates -
- low Hb - associated with increased risk of falls, and poor appetite and currently prescribed omeprazole.

Advisable to check plasma proteins (albumin, total proteins) as markers of nutritional status. The plasma proteins are the primary transporters for 3 of the prescribed drugs and hypoproteinaemia may alter their effects.

Glycaemia

Before breakfast - 6.9-12.1; recommended range 4-6.
Daily range - 6.9-19.9; recommended range 4-10.
Tested daily bd.
Reportable limits: < 4 and > 20/25.
"Old" HbA1c indicates poor glycaemic control - advisable to recheck status.

Mr ACS	Before breakfast BSLs	Before evening meal BSLs
Date	~ 07:30	~ 16:30
26/01	8.2	8.6
27/01	7.8	10.2
28/01	7.6	13.3
29/01	6.2	7.8
30/01	7.8	7.3
31/01	7.7	10.5
01/02	8.3	7.5
02/02	8.8	6.3
03/02	7.7	11.8
04/02	9.3	7.6
05/02	7.6	8.7
06/02	7.0	8.5
07/02	10.5	8.5
08/02	9.6	

Bolded BSLs WITHIN acceptable range

MEALTIMES:

Breakfast:	08:00	Morning tea:	10:00
Midday meal:	12:00	Afternoon tea:	15:00
Evening meal:	17:00	Supper: -	20:00

Diabetes drugs
Novomix 30 - (34U mane, 22U); has a time to onset of 5-15 minutes, variable time to peak, and duration 10-16 hours.
Metformin - has a duration of 12 hours.

Diabetes drugs coverage
- before breakfast BSLs - minimal, if any, coverage from previous morning's novomix 30 or previous evening's novomix 30, or previous morning's metformin;
- before evening meal BSLs - minimal, if any, coverage from previous evening's novomix 30; covered by current morning's novomix 30, and current morning's metformin.

Currently prescribed 3 medications that alter glycaemia

Pharmaconutrition

Currently prescribed

- 5 medications that include nausea and diarrhoea as side effects.
- 4 medications that include vomiting as a side effect.
- 3 medications that include constipation, altered taste and thiamine as side effects.

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

Metformin decreases absorption of B12, B1, B6, B9, Mg and Zn - there is now a recommendation for B12 levels to be monitored on a regular basis ie at least annually.

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

Regular monitoring sodium levels recommended whilst sertraline prescribed.

Currently prescribed two drugs that decrease B12 absorption - being metformin and omeprazole. Advisable to check B12 status and clarify current status.

Currently prescribed two drugs that decrease thiamine absorption - being metformin and omeprazole. The evidence is steadily increasing regarding the importance of thiamine in neurological safety and function, and in energy metabolism. Thiamine interventions should be administered with a magnesium intervention as magnesium is important in the activation of thiamine.

Currently prescribed two drugs that decrease magnesium absorption - being metformin and omeprazole.

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.

Several of Mr ACS's prescribed medications alter the functionality of the membrane transporters associated with thiamine, choline, carnitine, niacin, pyridoxine, pantothenate, folate. Their primary mechanisms of action include substrate

displacement and transporter inhibition. Consequently, blood test results are likely to be unreliable as the absorption and excretion of these nutrients is altered. Advisable for blood tests to be conducted before, or several hours after drug administration, to improve reliability of results.

Bowel management

Regular aperient prescribed – yes.
Oral PRN aperient prescribed - administered 1 x Dec, 2 x Nov, 1 x Oct.
Nurse Initiated interventions administered – no.

Staff comments

Staff advise Mr ACS mostly has breakfast.

Observations

Mr ACS was sound asleep when I went to speak to him - he did not waken.

Until recently Mr ACS remained weight stable about 112-113 kg, however recent weights are aberrant and require checking.

Pharmaconutrition comments

Mr ACS's diabetes management includes 2 drugs administered before breakfast, of which one has a duration of about 10-16 hours and one has a duration of about 12 hours, and one drug administered before evening meal that has a duration of about 10-16 hours, and it is this drug that is impacting on the before-breakfast glycaemia. Mr ACS's afternoon glycaemia is curious - realistically he should have very low BSLs because both prescribed diabetes management drugs administered in the morning are maximally effective in the afternoons, however his BSLs are mostly high therefore one should ask why and there seem to be 5 options -

1. the hyperglycaemic effects of the afternoon tea snack food, caffeine, and chlorogenic acid in the caffeine are sufficient to offset the hypoglycaemic effects of the drugs,
2. current medication management strategy is undermedicating glycaemic control,
3. current medication management strategy is overmedicating glycaemic control and causing release of stored glucose as a hypoglycaemia management strategy,
4. current medication management strategy is overmedicating glycaemic control and Mr ACS is grazing to offset the hypoglycaemic effect,
5. current medication management strategy is overmedicating glycaemic control and causing both the liver to release stored glucose and Mr ACS to graze.

Therefore advisable to review current diabetes management strategy.

Several of Mr ACS's diagnoses fit within the metabolic syndrome cluster. Metabolic syndrome is characterised by insulin resistance and consequent hyperinsulinaemia - hyperinsulinaemia is associated with increased appetite and consequent weight gain which then compounds the insulin resistance. Physiologically the body releases insulin once glucose is present in the bloodstream - the presence of insulin in the bloodstream at other times increases the risk of insulin resistance.

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

- vitamin D within acceptable range - currently no intervention. Early evidence indicates low vitamin D is a predictor of peripheral insulin resistance and elevated inflammatory response markers;
- magnesium – is important in glycaemic control; currently prescribed omeprazole which significantly decreases magnesium absorption, and currently no intervention. Advisable to review status;
- chromium - evidence indicates chromium both increases the number of insulin receptor cells on cell walls, and improves intracellular response to insulin. A short term (90-120 days) intervention of elemental chromium 500 mcg/day bd is likely to confer longterm benefit and is not associated with harm (a dose of 70 mg/day is required to cause harm);
- thiamine - people with diabetes have a significantly increased urinary excretion of thiamine; thiamine is important in glycaemic control; currently also prescribed metformin and omeprazole which further increases thiamine excretion. Advisable to consider short term (90-120 days), low dose (~ 10 mg/day) thiamine intervention on a regular basis such as annually
- biotin – 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;
- TNF-α – evidence indicates TNF- α has systemic effects that result in insulin resistance and NIDDM; low B12 status exacerbates elevated TNF- α and currently prescribed metformin and omeprazole therefore advisable to check B12 status
- zinc – 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) and currently prescribed omeprazole therefore advisable to check status.

Mr ACS has been prescribed a proton pump inhibitor for at least 4 years. 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;
- increasing 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;
- increased risk of dementia;
- 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 ACS's diagnoses include arthritis which is commonly associated with chronic pain - nutritional factors that may be useful to consider in pain management include -

- vitamin D – currently prescribed simvastatin therefore advisable to monitor vitamin D levels.

- 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.

- 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 vitamin C is not considered part of the pain management armament 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.

- 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 metformin and omeprazole which decrease magnesium availability.

Mr ACS's diagnoses include deafness - - nutritional factors that may be useful to consider in deafness management include –

- B12 and/or folate - currently prescribed metformin and esomeprazole therefore advisable to monitor B12 and folic acid and if low then intervention recommended;
- vitamin C - inadequate dietary intake associated with deafness; currently prescribed omeprazole which reduces conversion of vitamin C to its active form;
- vitamin D - associated with low-frequency and speech-frequency hearing loss; currently prescribed simvastatin therefore advisable to clarify status.;
- zinc - inadequate zinc status has been associated with impaired hearing; currently prescribed metformin and omeprazole 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 metformin, sertraline and omeprazole which decrease thiamine availability both directly and indirectly.

What else would you include?

Please read this as it is important …

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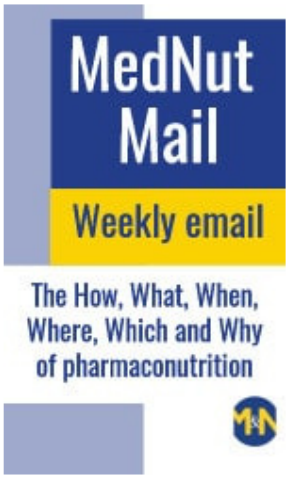

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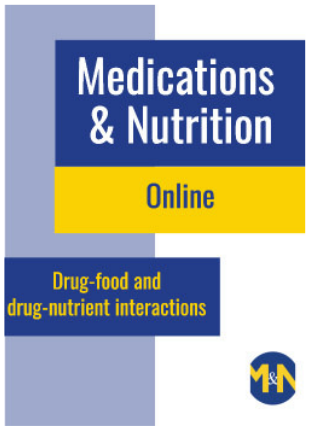

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