MedNut Mail

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

Warfarin and other nutrients

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Commentary

Warfarin is an anticoagulant for which there is a well-known coagulation interaction with vitamin K however its interactions with other nutrients are less well-known.

Warfarin is a substrate and inhibitor for the transporters OAT1/2, and it is carried in the blood by albumin and alpha-1 acid glycoprotein.

Transporters OAT1-4 mostly shuttle from blood into kidneys.

Warfarin also interacts with -

- choline – OAT1/3 substrate, OCT1/2/3 substrate and inhibitor;
- folic acid – OAT1 inhibitor;
- niacin – OAT2 inhibitor; a case study concluded that extended-release niacin may have enhanced the warfarin effect. Given that both are OAT2 inhibitors this is possible;
- melatonin – both are metabolized by cytochrome P450 isoform 3A4; concurrent administration resulted in altered coagulation status and therefore regular monitoring of PT and INR is recommended;
- vitamin C – OAT2 substrate. A case study concluded that ascorbic acid may have an inhibitory effect when administered concurrently with warfarin. Given that both are OAT2 substrates this is possible;
- pyridoxine - OAT1/3 substrate,
- vitamin D - mechanism is currently unknown, however its regulatory role in coagulation, endothelium homeostasis and inflammatory response results in a protective role against thrombosis. Evidence indicates those with adequate vitamin D status generally required lower doses of warfarin; there is a recommendation to check and treat vitamin D inadequacy in those requiring warfarin;
- pantothenic acid – OAT1 substrate;
- selenium – enhances warfarin effect and increases bleeding time,
- vitamin E - enhances warfarin effect and increases bleeding time,
- vitamin A - enhances warfarin effect and increases bleeding time,
- iodine – may alter (increase, decrease) warfarin effect,

- magnesium – proposed mechanism of action is that concurrent administration of warfarin and magnesium results in magnesium binding to warfarin and thus reduces its absorption – there is a recommendation that warfarin and magnesium be administered at significantly different times (≥ 2 hours);
- zinc – proposed mechanism of action is that concurrent administration of warfarin and zinc results in zinc binding to warfarin and thus reduces its absorption – there is a recommendation that warfarin and zinc be administered at significantly different times (≥ 2 hours)
- iron – proposed mechanism of action is that concurrent administration of warfarin and iron results in iron binding to warfarin and thus reduces its absorption – there is a recommendation that warfarin and iron be administered at significantly different times (≥ 2 hours).

When you see someone prescribed warfarin – will you -

- recommend checking albumin status if there is loss of weight?
- include the negative impacts of other prescribed medications on the nutrients that interact with warfarin in your clinical report?

Conclusions

Warfarin is a powerful anticoagulant that interacts with a broad spectrum of nutrients – most of which are not included in daily clinical practice guidelines – perhaps it's time they are.

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: hyperlipidaemia, asthma

Other: STML, chronic pain, vit D def, deafness, GORD

Biochemistry with Pharmaconutritional Consequences

Na:	142	mmol/l	Hb:	126	g/L	Albumin:	43	g/L	BSL:		mmol/l
K:	4.5	mmol/l	Lymph:	0.5		Total Protein:	67	g/L	HbA1C:		
Urea:	10.8	mmol/l	MCV:	97	mmol/l	B12:	636	pmol/L	INR:		
Creatinine:	0.068	mmol/l	Zn:		umol/l	Folate:	> 54.0	nmol/L	TSH:	2.24	mIU/L

Other: eGFR > 60, chol 5.2, Tg 7.7, Fe 13, TRF 3.0, satn 17%, ferritin 87, vit D 53

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
Aspirin	C, Fe	☑	NV				☐				☐	☐	☑
CALTRATE	Fe	☐		C			☐				☐	☐	☐
Cholecalciferol	(1/day)	☐					☐				☐	☐	☐
Folic Acid		☑					☐				☐	☐	☐
Irbesartan		☑	NV	CD	↑	↕	☑				☑	☑	☐
Mirtazapine		☐	N	D	↑	↑	☐				☑	☐	☐
NEO-B12	due 27/6/16	☐	NV	D			☐				☐	☐	☐
PANADOL OSTEO		☐	NV	CD			☐				☐	☐	☐
Risperidone		☑	NV	C	↑		☐		↑		☐	☐	☐
SOMAC	(40 mg/day) B1, B12, Ca, Fe,	☑	NV	CD		↓	☑				☑	☐	☐

Extra drug: thiamine (2/day)

Summary of medications, nutrients and transporters

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

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

Data summary

Biochemistry

Recent relevant biochemistry indicates -

- high-normal B12 levels - evidence indicates elevated B12 levels diminish cognitive function therefore advisable to check B12 levels prior to next scheduled injection, and if still within high-normal range then consider reducing frequency of interventions from 3-monthly to 6-monthly;

- elevated folate levels - evidence indicates elevated folate levels diminish cognitive function therefore advisable to review necessity for its continued prescription;

- marginal-low vitamin D - currently prescribed vitamin D (1 tab/day). Advisable to review current vitamin D management strategy and consider increasing level of intervention.

Glycaemia

Currently prescribed 2 medications that may alter glycaemia, being aspirin and risperidone.

Pharmaconutrition

Currently prescribed 7 medications that include nausea as a side effect.

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

Currently prescribed 5 medications that include constipation, diarrhoea, and

anaemia as side effects.

Currently prescribed 4 medications that alter iron status.

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

Calcium carbonate may interfere with the absorption of iron.

Calcium carbonate requires gastric acid for absorption however proton pump inhibitors such as esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole reduce gastric acid availability and therefore decrease calcium absorption, consequently calcium citrate preferred option as a calcium supplement as gastric acid not required for its absorption.

Irbesartan is likely to reduce zinc status in many but not all people with hypertension.

Regular monitoring sodium levels recommended whilst mirtazepine prescribed.

B12 administration will result in increased red cell production and consequently increase iron requirements - advisable to monitor iron status and correct iron deficiency.

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

Longterm pantoprazole use alters gut microbiome by increasing in Fimicutes and reducing Bacteriodetes

Concurrent ingestion of paracetamol and iron resulted 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.

Risperidone is associated with weight gain that is time and dose dependent - with a weight gain of about 2.6 kg in a year.

Somac 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 somac 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 current magnesium status.

Bowel management

- no regular interventions prescribed,

- oral PRN aperient prescribed; administered 2 x Apr, 2 x Mar, 2 x Feb,

- no Nurse Initiated interventions administered.

Staff comments

Staff advise Mrs ACG eats a good breakfast and has a variable and diminishing appetite at midday and evening meals.

Observations

Mrs ACG is currently weight stable.

Pharmaconutrition assessment

Mrs ACG has been prescribed a proton pump inhibitor since admission 3 years ago, and likely before then. 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 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).

Thiamine (200 mg/day) has been prescribed for at least 3 months and likely longer. The estimated average requirement (per day) for an adult aged 70+ years is 0.9 mg/day, and the Recommended Dietary Intake (per day) is 1.1 mg/day. Mrs ACG's diagnoses do not include alcohol abuse, or other significantly-thiamine-depleting disorders. There is increasing evidence that long-term high-dose water soluble

vitamin interventions can cause harm and examples include -

- pyridoxine - doses > 10 x RDI associated with irreversible peripheral neuropathy,
- B12 - excessive intake associated with cognitive impairment,
- folate - excessive intake associated with cognitive impairment.

It also appears that the prescription of thiamine is a transcription error. Mrs ACG was prescribed 2 x pyridoxine tabs/day (50 mg pyridoxine/day) for at least for 2½ years - this intervention was not formally ceased; Mrs ACG was then prescribed 2 x thiamine tabs/day (200 mg thiamine/day) - a prescription that remains current.

Therefore, advisable to review necessity for ongoing prescription of thiamine and consider its immediate cessation.

Mrs ACG's diagnoses include chronic pain - nutritional factors that may be useful to consider in pain management include -

- vitamin D - current intervention may not be adequate to attain adequate range. Evidence indicates increasingly brittle pain control with decreasing vitamin D levels. Last measurement indicated vitamin D status at lower end of (bone health) acceptable range therefore advisable to check vitamin D levels and if still low or marginally low then review current vitamin D management strategy.

- 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. 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 aspirin and pantoprazole which decrease 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 pantoprazole therefore advisable to monitor 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 pantoprazole which decreases magnesium absorption therefore advisable to clarify status.

Mrs ACG'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 pantoprazole therefore advisable to check B12 status and if low then intervention recommended;
- vitamin C - inadequate dietary intake associated with deafness; currently prescribed aspirin and pantoprazole which reduces conversion of vitamin C to its active form;
- vitamin D - associated with low-frequency and speech-frequency hearing loss; currently prescribed an intervention and current status is marginal therefore advisable to monitor status;
- zinc - inadequate zinc status has been associated with impaired hearing; currently prescribed pantoprazole therefore advisable to check zinc status and if low then intervention recommended;
- Thiamine – associated with bilateral hearing loss; currently prescribed pantoprazole and thiamine intervention therefore advisable to clarify thiamine status.

Mrs ACG's diagnoses include osteoporosis – nutritional factors that may be useful to consider in bone health management include -

Nutrients with U-curved impacts in bone health ie both positive and negative impacts, include –

Iron – is important in bone homeostasis and remodelling; both inadequate and excessive intakes associated with impaired bone structural integrity; currently prescribed aspirin, calcium carbonate and pantoprazole therefore advisable to monitor status.

Nutrients with positive impacts in bone health include –

Cobalamin (B12) – is important in osteoblast activity, and bone strength; currently prescribed pantoprazole therefore advisable to monitor status;

Vitamin C – is important in collagen formation, osteoblast synthesis, osteoclast suppression, reducing oxidative stress, regenerating vitamin E; increased intake is associated with increased bone density. Currently prescribed aspirin and pantoprazole therefore advisable to monitor status;

Vitamin D – is important in bone mineralization, regulating calcium absorption, regulating bone and renal resorption, parathyroid synthesis, bone

strength; currently prescribed an intervention therefore advisable to monitor status and clarify effectiveness of the intervention;

Calcium – is important in skeletal development and growth, and bone mineralization. Currently prescribed an intervention that may not be effective as pantoprazole also prescribed therefore advisable to review current calcium intervention;

Magnesium – is important in cellular energy generation, bone formation and mineralization, calcium homeostasis, inflammatory response and endothelial function with resultant decreased osteoclastic and osteoblastic activity, osteopenia and skeletal fragility. Currently prescribed pantoprazole therefore advisable to clarify status;

Zinc – is important as a cofactor for many metalloproteins involved in bone development. Currently prescribed pantoprazole therefore advisable to clarify status;

Nutrients with negative impacts in bone health include –

Sodium – excessive intake competes with calcium for reabsorption in the renal tubules ie excessive sodium intake increases calcium loss. Currently prescribed pantoprazole which decreases sodium availability therefore advisable to monitor status.

What else would you include?

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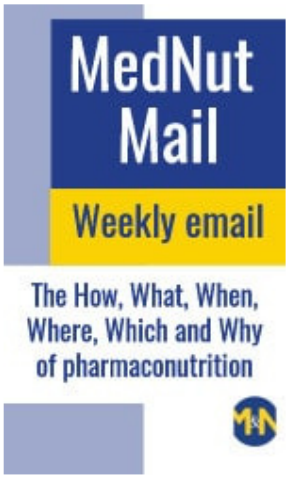

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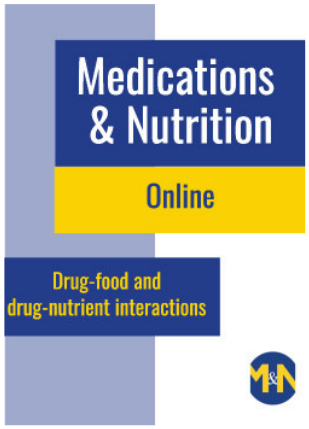

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