MedNut Mail

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

Warfarin-food interactions

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28th November 2022

https://medicationsandnutrition.online

Commentary

The warfarin-vitamin K interaction is well-known and so those prescribed warfarin are typically "educated" about vitamin K containing foodstuffs, however there is minimal advice regarding warfarin interactions with other foodstuffs.

Whilst some warfarin-food interactions are related to Vitamin K content there are other interactions with alternate mechanisms of action.

Vitamin K content – inhibits coagulation

- **Avocado** - has a lower vitamin K content (~ 20 mcg/100g), its warfarin-antagonising effect is possibly due to an alternate mechanism.
- **Black tea** – proposed mechanism is vitamin K content and that sufficient quantities may suppress INR however vitamin K content on the Food Data Central database (https://fdc.nal.usda.gov/fdc-app.html#/food-details/2346058/nutrients) is zero, therefore likely mechanism of action is unknown.
- **Green tea** – proposed mechanism is vitamin K content however vitamin K content on the Food Data Central database (https://fdc.nal.usda.gov/fdc-app.html#/food-details/2346058/nutrients) is zero, also not associated with cytochrome P450 pathway isozyme 2C9 therefore mechanism of action is currently unknown.

Anticoagulation

- Natural sources of coumarins include vegetables such as cabbage, radish, spinach, Tonka beans, melilot, woodruff and ginkgo (some claim no effect with gingko).
- Omega-3 polyunsaturated fatty acids (fish oils) reduces coagulation, thrombosis, etc through the coagulation cascade.

Cytochrome P450 (CYP 450)

- **Cranberry juice** - contradictory advice for the last couple decades regarding the mechanism of action. I am uncertain how much is due to recycling of the (very limited) research and how much is due to inconsistencies in research (comparing apples with pineapples), however both are associated with the CYP450 3A4 and 2C9 isoforms.
- **Grapefruit juice** – contradictory advice for the last couple decades regarding the mechanism of action. I am uncertain how much is due to recycling of the

(limited) research and how much is due to inconsistencies in research (comparing apples with pineapples), however both are associated with the CYP450 3A4, 2A6 an 1A2 isoforms.

- **Pomegranate juice** - contradictory advice for the last couple decades regarding the mechanism of action based on **very** limited evidence; proposed mechanisms - association with CYP P450 3A, 3A4 and 2C9 isoforms.
- **Maitake mushroom** – very limited evidence; speculative mechanism of action.
- **Mango** – very limited evidence; proposed mechanism – Vitamin A (within the fruit) inhibits CYP 2C19 isoform.
- **Melatonin -** concurrent use of melatonin and warfarin may impact INR and PT and therefore affect coagulation status, consequently regular monitoring of PT and INR is recommended. Both melatonin and warfarin are metabolised by CYP 3A4, 2C19, CYP1A2, and possibly 2C9 isoforms, and melatonin also inhibits CYP 1A2 isoform. Likely mechanisms of action include interaction with in-common metabolic cytochromes and/or altering Factor VIII and fibrinogen status. This 2021 article (DOI: 10.1039/d0fo03213a) has an excellent table identifying melatonin content of plant foods, and the article (doi:10.3390/nu9040367) has a reasonable summary of a broader selection of foods.
- **Quinine** - potentiates anticoagulation. Seemingly quinine and warfarin have many CYPs in common, and both share, compete for, and inhibit their functions with the end result likely being more warfarin in the blood -

	Substrate	inhibitor	inducer
3A4	quinine warfarin	quinine	quinine
1A2	quinine warfarin		
2C8	quinine warfarin	quinine	
2C9	quinine warfarin		warfarin
2C19	quinine warfarin	quinine warfarin	

Since quinine is an inhibitor and/or substrate for several Organic Cation Transports, including OCT1 and OCT2 there is a possibility for quinine to alter

liver and renal uptake of some foodstuff nutrients and thus indirectly alter coagulation status. Food sources of quinine include tonic drinks, bitter drinks, quinine drinks and alcoholic beverages.

- **Xanthines** - antagonise anticoagulation; likely mechanism of action is as a substrate for CYP 1A2 isoform. Primary xanthine food sources include tea, coffee, cola, chocolate, cocoa, some carbonated drinks, guarana, cola nuts.

Other

- **Chlorinated pesticides** - decrease warfarin effect. The evidence in relation to this finding is proving difficult to locate therefore it is difficult to ascertain the probable mechanism(s) of action. Further, the main issue arising is the question "should organic foods be recommended given this is a likely presence or absence response rather than a dose-related response?" and the current answer is "don't know".
- **Alcoholic beverages** - heavy chronic alcohol intake may decrease drug effect; acute intake may increase drug effect; moderate intake may not alter drug status.
- **Protein intake** – changes in protein status and protein intake can alter warfarin effect. Warfarin is highly bound to albumin (protein carrier) with the "free" component being therapeutic – changes to protein intake that alter albumin status are likely to alter warfarin intake.
- **Salicylates** - potentiate anticoagulation; proposed mechanism of action is that salicylates have a higher affinity for protein binding sites than does warfarin. Given many commonly consumed fruits and vegetables contain significant vitamin K it seems likely other/alternate mechanisms of action include vitamin K content, and probably some of the CYP 450's and "drug" transporters.

Most research focuses on the impact of food on warfarin however no-one considers warfarin altering food factors – especially nutrient uptake. For example, many salicylates potentiate anticoagulation, however they are mostly good sources of Vitamin C – both warfarin and Vitamin C are substrates for the transporter OAT2 (from blood into kidneys) therefore it is likely there will be competition for renal uptake, and whichever one does not board the transporter remains in the blood for a longer period.

What actions will you initiate when you see a person prescribed warfarin – will you –

- review their daily dietary habit with regard to adequacy and stability of Vitamin K intake?

- Review their dietary habit with regard to frequency and impact of “special extras”?
- recommend a gap between food intake and warfarin administration?

Conclusions

Warfarin is a very powerful medicine that interacts with a range of metabolic processes that may ultimately alter the consumer’s nutritional status and consequent health outcome – many of these interactions have been identified on a case study basis and so are currently not considered clinically significant and consequently disregarded; case studies are usually the canary in the coal mine.

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: cellulitis, chronic leg ulcer, GORD, lymphoedema

Biochemistry with Pharmaconutritional Consequences

Na:	140	mmol/l	Hb:	113	g/L	Albumin:		g/L	BSL:		mmol/l
K:	4.8	mmol/l	Lymph:	1.5		Total Protein:		g/L	HbA1C:	6.8	
Urea:	21.4	mmol/l	MCV:	91	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.213	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR 18, chol 3.9, Tg 1.4

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
AVAPRO HCT	Ca, Cl, K, Mg, Na		☑	NV	CD	↑	↓	☑				☑	☑	☐
DIAMICRON MR	(12:00)		☑	NV	CD	↑	↕	☑				☐	☐	☑
FERRO-F	Ca, Mg, Zn		☐					☐				☐	☐	☐
Frusemide	(40 mg/day) Ca, Cl, K, Mg, Na,		☑	NV	CD		↓	☐				☑	☐	☑
Omeprazole	(20 mg/day) B1, B12, Ca, Fe,		☑	NV	CD	↑		☑				☑	☐	☐
OSTEVIT-D	(2/day)		☐					☐				☐	☐	☐
Pravastatin			☐	NV	CD	↕	↓	☑				☐	☐	☐
Prazosin			☑	NV	CD			☐				☑	☐	☑
Sertraline	Na		☑	NV	CD	↑	↑	☐				☑	☐	☐

Extra drug: lantus 4U mane, 8U nocte

Summary of medications, nutrients and transporters

Organ (transporter)	Thiamine	Choline	Carnitine	Pyridoxine
Inhibitor function				
From gut to epithelium	sertraline (THTR2)	sertraline (THTR2)		sertraline (THTR2)
Liver	omeprazole (OCT1) prazosin (OCT1) sertraline (OCT1)	omeprazole (OCT1) prazosin (OCT1) sertraline (OCT1)		
Into kidneys	omeprazole (OCT2) prazosin (OCT2) sertraline (OCT2)	omeprazole (OCT2) prazosin (OCT2) sertraline (OCT2)		
From kidneys to urine				
Into muscles	omeprazole (OCT3)	omeprazole (OCT3)	omeprazole (OCT3)	
Substrate function				
Liver	prazosin (OCT1)	prazosin (OCT1)		
Into muscles	prazosin (OCT3) sertraline (OCT3)	prazosin (OCT3) sertraline (OCT3)	prazosin (OCT3) sertraline (OCT3)	

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

Data summary

Biochemistry

Recent relevant biochemistry indicates

- low Hb – currently prescribed omeprazole; associated with increased risk of falls, and poor appetite.

Advisable to check plasma proteins (albumin, total proteins) as they are the primary transporters for six of the prescribed drugs and hypoproteinaemia may alter their effects and side effects.

Glycaemia

BSLs (Jun-Jul) -

- before breakfast - 3.1-7.2; recommended range 4-6;

- daily range - 3.1-19.8; recommended range 4-10;

- tested daily bd;

- reportable limits: < 4 and > 16;

- recent HbA1c indicates good glycaemic control.

Diabetes drugs

- lantus has a time to onset of 1hour, minimal peak, and duration of 20-26 hours;

- diamicron has a duration of 18-24 hours.

Diabetes drugs coverage

- before breakfast BSLs - minimal, if any, coverage from previous morning's lantus, or previous midday diamicron; covered by previous evening's lantus;

- before evening meal BSLs - minimal, if any, coverage from previous evening's lantus; covered by current morning's lantus, and current midday diamicron.

Currently prescribed 4 medications that may alter glycaemia.

Pharmaconutrition

Currently prescribed 4 medications that alter zinc status as a side effect.

Currently prescribed 4 medications that include altered taste as a side effect.

Currently prescribed 5 medications that include hyponatraemia as a side effect.

Currently prescribed 5 medications that include dry mouth as a side effect.

Currently prescribed 7 medications that include nausea, vomiting, constipation and diarrhoea as side effects.

Avapro HCT associated with decreased magnesium and zinc status.

Urinary thiamine losses have been indicated with almost all diuretics including avapro HCT and frusemide.

Ferro-F contains folic acid; evidence indicates elevated folic acid levels can impair cognitive function therefore advisable to monitor status.

Ferro-F decreases zinc absorption.

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

Gliclazide decreases B12 availability.

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

Regular monitoring sodium levels recommended whilst Avapro HCT and sertraline prescribed.

Currently prescribed ostevit (2/day). Advisable to check vitamin D levels and if still low then review current vitamin D management strategy

Currently prescribed the daily double ie two drugs that decrease magnesium availability - being frusemide and omeprazole. 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 magnesium status.

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.

Bowel management

- no regular interventions prescribed,

- no PRN interventions prescribed,

- no Nurse Initiated interventions administered.

Staff comments

Staff advise Mrs AGH refuses to eat hot meals.

Observations

Mrs AGH is a small, pale, charming lady who was sitting in the Day Room when I went to speak to her - she told me she does not feel like a hot meal at midday as it is too soon after breakfast, and that she eats sandwiches and dessert at midday; she assured me she eats the evening meal.

Mrs AGH has remained weight stable for the last 6 months; frusemide dose has not changed since admission.

Pharmaconutrition comments

Mrs AGH is pale, and is prescribed an iron supplement and a proton pump inhibitor - it is likely the proton pump inhibitor is minimising the effectiveness of the iron supplement; low iron levels can diminish appetite.

Assessment

Mrs AGH has had several low BSL readings before breakfast - advisable to clarify that she is eating a reasonable supper and if so then advisable to review evening lantus

dose.

As Mrs AGH's cholesterol levels are well within acceptable range, and now that she is not eating quite as well, and given statin side effects include poor appetite, advisable to review necessity for continued pravastatin prescription.

Some of Mrs AGH'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 strategies 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. Advisable to clarify current status;

- 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. Advisable to consider a short term (90-120 days) intervention however given omeprazole prescribed there may be limited benefit;

- thiamine - is important in glycaemic control; currently prescribed frusemide which increases thiamine excretion and omeprazole which decreases thiamine availability. A periodic short term (90-120 days), low dose (~ 10 mg/day) thiamine intervention may confer benefit;

- 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 t and currently prescribed gliclazide and omeprazole therefore advisable to clarify B12 status.

Mrs AGH'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. Currently prescribed pravastatin which decreases vitamin D status. Advisable to

check vitamin D levels and if still 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. Currently prescribed omeprazole which decreases conversion of vitamin C to its active form therefore advisable to consider a vitamin C intervention.

- 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 gliclazide and omeprazole 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 frusemide and omeprazole both of which decrease magnesium availability.

What else would you include?

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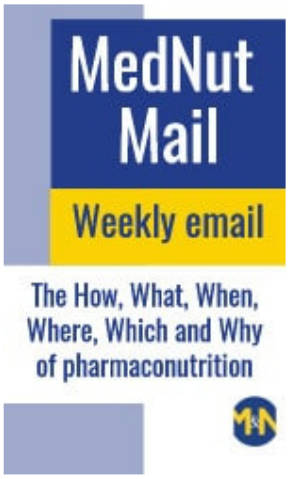

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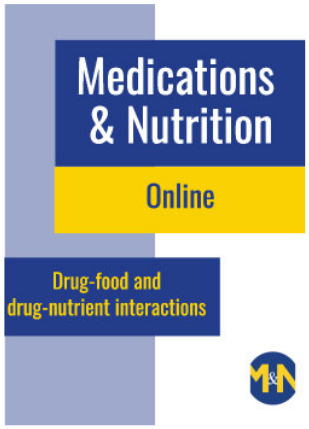

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