MedNut Mail

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

Drug interactions and pharmaconutrition

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https://medicationsandnutrition.online

Commentary

Medications, medicines, drugs are used interchangeably to describe chemical substances that are administered to confer therapeutic benefit; they interact with 3 key groups –

- **Other medicines** – aka drug-drug interactions,
- **Nutrients** – aka drug-nutrient interactions,
- **Foods** – aka drug-food interactions.

Drug-drug interactions are well researched, and many facets of these interactions are included in the drug discovery process. The combination of the FDA (Food and Drug Administration) policy to reduce drug-drug interactions and the desire of the pharmaceutical companies to access currently inaccessible body areas has resulted in extensive research in "drug" transporters ie physiological transporters that are utilized by nutritive substances.

Until the early 1990's the pharmaceutical sector considered food to be "benign" and their issue was whether to administer their drugs prior to food to maximize therapeutic benefit or with food to minimize side effects. Then in the early 1990's a Canadian research team investigating felodipine/nifedipine interactions with alcohol discovered the grapefruit effect – subsequent research identified the key mechanism to be cytochrome (CYP) P450 isoform 3A4 and interactions with it are now part of the drug discovery process. No-one investigated which other foods also alter drug effect and 30 years later we still don't have a comprehensive database on drug-food interactions.

Drug-nutrient interactions were also disregarded until 2012 when early clinical trials found that within several months of administration the then new drug fedratinib caused Wernicke's Syndrome as it inhibited all the thiamine transporters ie absorption, distribution and excretion, and so it was not released. For some reason the metformin-B12 interaction remains "ignored" even with 60 years of evidence.

As the "drug" transporters research progresses, it is likely many currently unrecognized drug-nutrient interactions will be identified. In order to modify the negative impact of prescribed medications we do require our nutrition scientists to be clarifying issues such as -

- the degree of negative impact of each prescribed medicine,
- the best time to administer nutrient interventions, and
- the optimal nutrient dose to be administered.

Drug-food interactions have continued to be disregarded, even with the grapefruit findings and it is worthwhile pondering "why?". Pharmaceutical research is based on many knowns – the amount of the therapeutic substance, and the functions and effects of the excipients (ingredients) associated with the therapeutic substance – their main unknown is individual physiological response which is governed by genetic and environmental factors.

Food research starts from a very complex base that is influenced by -

- geographic location which influences nutrient content,
- localized climate which influences protein content,
- foodstuff genetics which influence responses to their environment and their uptake of nutrients,
- cultural and social factors which influence food choices and meal combinations.

So when food intake is associated with an altered response to a pharmaceutical intervention then the question is - is it caused by a pharmaceutical factor or a food factor? and how do we clarify the cause?

We do know about some single drug-food interactions – with alcoholic beverages, with grapefruit, and some related to caffeine. Perhaps the starting point is identifying interactions with a comprehensive range of single foodstuffs, and then as the expertise increases, we could consider more complex foodstuffs. Doing nothing because it is too difficult is unacceptable.

In order to encourage increased research in the areas of drug-nutrient and drug-food interactions, will you write to –

- the FDA (US regulatory body) and TGA (Australian regulatory body) to comment on the paucity of research in relation to these areas of significant interactions and request they be moved this up the priority ladder?
- your professional body and suggest these areas be prioritized in student projects
- your local Members of Parliament (House of Representatives and Senate, State and Federal) and request these areas be prioritized?

Conclusion

Although there are 3 key pharmaceutical interactions, being drug-drug interactions, drug-nutrient interactions and drug-food interactions, only drug-drug interactions attract significant research interest. Seemingly drug-food interactions are far more difficult than for example landing a man on the moon.

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: Renal transplant

Other: DVTs, Ca lung + bony mets, deafness

Biochemistry with Pharmaconutritional Consequences

Na:	133	mmol/l	Hb:	83	g/L	Albumin:	36	g/L	BSL:		mmol/l
K:	4.8	mmol/l	Lymph:	0.5		Total Protein:	66	g/L	HbA1C:		
Urea:	11.0	mmol/l	MCV:	108	mmol/l	B12:	1193	pmol/L	INR:		
Creatinine:	0.114	mmol/l	Zn:		umol/l	Folate:	42.1	nmol/L	TSH:		mIU/L

Other: eGFR 7, U alb 7, U creat 3.5, U alb:creat 2.0, CRP 118, ESR 95, Fe 10, TRF 1.6, satn 25%, ferritin 3894, Mg 0.95

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
Amitriptyline	B2		☑	NV	CD	↑	↑	☑		↓		☑	☐	☑
Esomeprazole	(40 mg/day) B1, B12, Ca, Fe,		☑	NV	CD	↑		☑				☑	☐	☐
Frusemide	(60 mg/day) Ca, Cl, K, Mg, Na,		☑	NV	CD		↓	☐				☑	☐	☑
Gliclazide	(08:00)		☑	NV	CD	↑	↕	☑				☐	☐	☑
Prednisolone	(08:00, 17:00) Ca, Cr, D, Iodin		☑	NV	CD	↕	↑	☐				☐	☐	☑
Spironolactone	K, Mg		☑	NV	D			☐				☐	☐	☐
Tacrolimus			☑	NV	CD		↕	☐				☐	☐	☑
TARGIN			☐	NV	CD		↕	☑				☑	☑	☐

Extra drug: linagliptin (08:00), aranesp, enoxaparin

Summary of medications, nutrients and transporters

Organ (transporter)	Thiamine	Choline	Pyridoxine
Inhibitor function			
From gut to epithelium	Amitriptyline (THTR2)		
Liver	Amitriptyline (OCT1) Esomeprazole (OCT1) Spironolactone (OCT1)	Amitriptyline (OCT1) Esomeprazole (OCT1) Spironolactone (OCT1)	
Into kidneys	Amitriptyline (OCT2) Prednisolone (OCT2) Spironolactone (OCT2) Naloxone (OCT2)	Prednisolone (OCT2) Spironolactone (OCT2) Naloxone (OCT2)	
From kidneys to urine			Amitriptyline (THTR2)
Into retina	Amitriptyline (OCT1)		
Substrate function			
Into muscles	Amitriptyline (OCT3)	Amitriptyline (OCT3)	

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

Data summary

Biochemistry

Recent relevant biochemistry indicates

- low sodium – currently prescribed SSRI prescription, SIADH; advisable to recheck status;

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

- elevated B12 - evidence indicates elevated B12 levels diminish cognitive function; currently not prescribed a B12 intervention - ? prescribed historically;

- elevated ferritin - typically indicates mobilisation of the storage form of iron to the active form due to inadequate iron availability; currently prescribed esomeprazole.

Glycaemia

- before breakfast - 5.0-8.2, mostly 5-7; recommended range 4-6

- tested weekly

Diabetes drugs

- gliclazide has a duration of 18-24

hours

- linagliptin has a duration of 24 hours

Diabetes drugs coverage

- before breakfast BSLs - minimal, if any, coverage from previous morning's gliclazide or linagliptin;

- before evening meal BSLs - covered by current morning's gliclazide and linagliptin.

Currently prescribed 4 medications that include may alter glycaemia, being amitriptyline, frusemide, prednisolone and tacrolimus.

Prednisolone induces hyperglycaemia in the afternoon and evening but not overnight, consequently hyperglycaemia management strategies should target the timeframe from midday to midnight.

Pharmaconutrition

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

Currently prescribed 6 medications that include nausea, vomiting and diarrhoea as side effects.

Currently prescribed 4 medications that include altered taste and dry mouth as side effects.

Phenothiazine derivatives such as amitriptyline are similar in structure to vitamin B2 (riboflavin) and consequently decrease riboflavin availability.

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

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

Evidence indicates that glucocorticoids such as prednisolone are associated with lower vitamin D levels; proposed mechanism steroids may enhance inactivation of vitamin D-2 by upregulating 24-hydroxylase activity.

Urinary thiamine losses have been indicated with almost all diuretics including spironolactone.

Spironolactone impairs zinc status.

Tacrolimus reduces intracellular magnesium levels: proposed mechanism - drug-induced suppression of vitamin D receptor expression.

Currently prescribed the trifecta ie three drugs that decrease magnesium availability - being esomeprazole, frusemide, and tacrolimus. Magnesium deficiency manifests as confusion, disorientation, personality changes, loss of appetite, depression, muscle cramps, tingling, numbness, hypertension, cardiac dysrhythmia, seizures. 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.

Bowel management

- no regular intervention prescribed,

- oral PRN aperient prescribed,

- no Nurse Initiated interventions administered.

Staff comments

Staff advise Mr ACE eats well.

Observations

Mr ACE is a tall, big-framed, pale, breathless man with thyroidy eyes, a large abdo, and scrawny shoulders - he told me the food has a bitter and/or metallic taste and attributes it to the chemo. Mr ACE also told me he wishes to be provided regular meals as he was a sympathy-vegetarian to support his wife. Mr ACE also told me he enjoys milkshakes.

Mr ACE was weight stable at admission and is now losing weight.

Assessment

Mr ACE has lost weight. Loss of weight is associated with depletion of zinc status and zinc is important in a range of body functions, including sense of taste and release of the hunger hormone Neuropeptide Y. Since Mr ACE has lost weight, advisable to check zinc levels and if inadequate then short term (90-120 days) intervention and recheck status prior to cessation of the intervention; however currently prescribed esomeprazole which may reduce the effectiveness of the intervention.

Mr ACE'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 prednisolone 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. Advisable to consider a vitamin C intervention - the optimal intervention is 500 mg vitamin C/day (if more than 500 mg vitamin C administered at a time then the excess above 500 mg is not absorbed as the vitamin C transporters are overloaded). 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 esomeprazole 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 esomeprazole 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 esomeprazole and frusemide which decrease magnesium absorption. Advisable to clarify magnesium status.

Mr ACE'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 esomeprazole therefore advisable to check B12 status and if low then intervention recommended;
- vitamin C - inadequate dietary intake associated with deafness; currently prescribed esomeprazole which reduces conversion of vitamin C to its active form;
- vitamin D - associated with low-frequency and speech-frequency hearing loss; currently prescribed prednisolone therefore advisable to clarify status.;
- zinc - inadequate zinc status has been associated with impaired hearing; currently prescribed esomeprazole 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 esomeprazole and frusemide which decrease thiamine availability both directly and indirectly.

What else would you include?

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.

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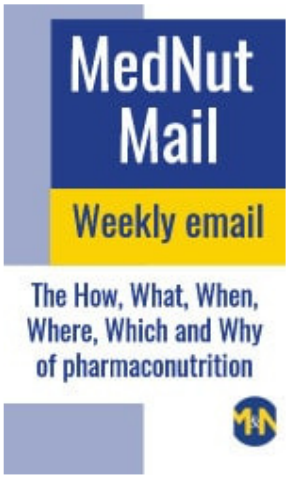

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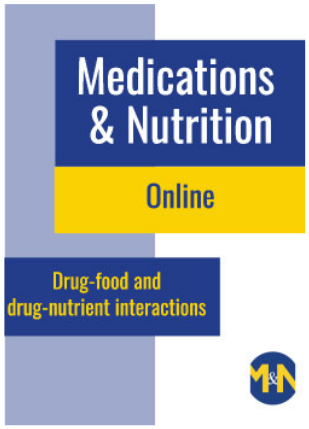

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