MedNut Mail

The How, What, Which, Where, When and Why of pharmaconutrition

Not clinically relevant

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Editorial

“Not clinically relevant”, “inhibition unlikely at therapeutic interventions”, “clinical inhibition deemed minimal”, and similar other phrases typically refer to drug-transporter interactions; the phrases such as “at this dose” or similar, are also generally included and all relate to drug-drug interactions only. From a nutrition perspective, these phrases are red flags as indirect nutrition impacts are likely, primarily via the drug-transporter interaction pathways.

Whilst there are hundreds of transporters operating in the body, our knowledge is limited to a very small number, of which an even smaller number are included in the drug discovery process. Much of the research evidence is driven by the pharmaceutical sector as they seek mechanisms to gain access to the parts of the body currently unavailable to them – and transporters are seen as a likely success vehicle.

But, and sadly it is a big but, our knowledge on the full range of functions of the identified transporters is still remarkably limited – especially since a lot of the research is still focused on 3 key areas, being (i) trying to find reliable test substances, (ii) identifying new transporters and whether they are fit for (pharmaceutical) purpose, and (iii) establishing whether/which *in vitro* tests are as reliable as *in vivo* tests. Many of the testing techniques are yet to be standardized so it is likely current findings will be modified as our knowledge expands.

As there is minimal, if any, nutrition science representation in the pharmaceutical regulatory bodies, and as there are no regulatory requirements that drug impacts on nutrition factors be included in the drug discovery process, and as our nutrition scientists seem to be busy elsewhere, it seems this aspect of likely mal-nutrition will remain overlooked.

So, when our red flag is waving with phrases such as - “Not clinically relevant” - what strategies or actions should we initiate from a nutrition perspective to minimize nutritional harm? I suggest that if blood tests are not congruent with Diet History conclusions, then we have to assume pharmaceutical-induced nutritional harm. For example, if a person has a low, high-normal or elevated blood test result, the nutrient is not stored in the bones (constant bone-remodelling means ongoing flux of nutrients and toxic metals), and the Diet History indicates an adequate dietary intake, then the logical conclusion is that harm is being caused by the prescribed

medicine inhibiting the nutrient's transporter(s) – whether it is transfer into the blood or into the organs and cells.

There are 3 key areas for which we really need answers -

1. **Substrates**. We really need to know -

- the turnaround time of transporters from pick-up to drop-off and return,

- load capacity of each transporter - for example load capacity for SVCT (Sodium Vitamin C Transporter) is a maximum of 500 mg,

- each medicine's optimal administration time in relation to meals in order to minimize negative impact on nutrient absorption during digestion,

- whether the transport of medicines and nutrients is of the same duration,

- whether transporters can carry several different substrates at the same time;

2. **Drug-induced duration of inhibition**. We really need to know -

- whether the duration of inhibition is related to the time to drug elimination (typically 5-6 times the half-life), or whether it is related to the duration of therapeutic benefit which can be hours or days,

- whether medicines and nutrients have different durations of inhibition from each other,

- whether several different inhibitors can impact at the same time and whether the inhibition is additive or concurrent;

3. **Nutrient-induced duration of inhibition.** We really need to know -

- the factors that stimulate nutrients to inhibit their transporters,

- duration of nutrient-induced inhibition,

- whether the duration of inhibition is dependent upon dose,

- whether the inhibition is additive or concurrent with other inhibitors.

The problem then becomes one of determining the best time to administer nutrient interventions in relation to drug administration. In the absence of evidence, I suggest nutrient interventions be administered one to two hours prior to administration of prescribed medicines - which may not be practical for those dependent upon others for the administration of their medicines.

Clinical Questions

What actions will you initiate when you see someone whose prescribed medicines may be vehicles of nutrient compromise, will you –

- ensure your Diet History is sufficiently thorough to establish adequacy of intake especially of those potentially compromised nutrients?
- review blood test results and clarify whether the Diet History and blood test results are congruent?
- advise the weekly Team Meeting of the increased risk of mal-nutrition as a consequence of a drug-nutrient interaction via the transporter network?
- recommend the Medications Advisory Committee develop management guidelines in relation to this issue, and have them distributed to all the Medical and Allied Health service providers to that facility?
- advise an appropriate administration time if a nutrient intervention is considered necessary?

Conclusions

“Not clinically relevant” and similar phrases are only applicable to drug-drug interactions, however there are likely to be significant nutritional consequences; there is very limited evidence currently available to guide our clinical decision-making in relation to pharmaceutically-induced negative impacts on nutrition.

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: tinnitus, vertigo, AF, deafness, CRF, vit D def

Other: Ca bowel - > hemicolectomy, hypercholesterolaemia

Biochemistry with Pharmaconutrition Consequences

Na:	140	mmol/l	Hb:	121	g/L	Albumin:	34	g/L	BSL:		mmol/l
K:	4.7	mmol/l	Lymph:	1.3		Total Protein:	63	g/L	HbA1C:		
Urea:	8.8	mmol/l	MCV:	92	mmol/l	B12:	190	pmol/L	INR:		
Creatinine:	0.072	mmol/l	Zn:		umol/l	Folate:	10.1	nmol/L	TSH:	0.38	mIU/L

Other: eGFR 60, ESR 10, CRP < 5, active B12 49, vit D 11, Ca 2.55, Ca corr 2.64, Fe 14, TRF 2.2, satn 25%, ferritin 166

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
Cholecalciferol	(50,000 IU/month)		☐					☐				☐	☐	☐
TENSIG	B2		☐	NV	CD			☐				☑	☐	☑

Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		MATE1		MATE2	
Nutrients - Sub	B1, choline, carnitine		B1, choline, NMN, carnitine		B1, NMN		B1, NMN, carnitine	
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Atenolol	Y		Y		Y	Y	Y	Y
Colecalciferol								

Comments – medication and nutrition effects only

Data summary

Biochemistry

Relevant available biochemistry indicates -

- marginal TSH - there is disagreement between pathology ranges and research findings with regard to appropriate TSH levels therefore advisable to recheck status;

- low vit D - commenced intervention 50,000 IU/month; advisable to recheck status and ensure intervention has been effective.

Glycaemia

BSLs

- tested monthly - last checked 2 months ago,

- HA1c 3/12 - last HbA1c checked – indeterminate,

- advisable to check HbA1c and clarify overall glycaemic control.

Pharmaconutrition

Tensig side effects include increased risk of diabetes and altered thyroid function.

Apple juice reduces Tensig availability.

Coffee inhibits vitamin D uptake by osteoblasts (bone builders).

Bowel management

No regular intervention prescribed.

Oral PRN aperient prescribed; administered 4 x Jun.

No Nurse Initiated interventions administered.

Staff comments

Staff advise variable appetite - eating well some days and not on other days.

Observations

Mrs ACL is a small, pale, frail lady who was sleeping in bed when I went to speak to her - I did not disturb her.

Mrs ACL has remained weight stable about 39-40 kg for the last 6 months.

Pharmaconutrition comments

Riboflavin is the rate limiter for one carbon metabolism, a pathway that intersects with a broad range of other metabolic pathways, and so there are likely significant flow-on effects.

Riboflavin is important for the activation of pyridoxine which in turn is important in the activation of niacin therefore inadequate riboflavin availability means utilisation of alternate energy pathways from oxidative phosphorylation, and probable increased nutrient requirements.

The identified membrane transporters inhibit the absorption and/or organ and cellular uptake of thiamine, choline, carnitine and niacin which means blood test results are likely to indicate normal or elevated status whereas these nutrients may be in the blood because they are prevented from entering relevant organs and cells. Advisable for blood tests to be conducted several hours after administration of relevant prescribed medicines.

What else would you include?

Not clinically relevant

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.

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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