MedNut Mail

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

Membrane transporters and pharmaconutrition

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Editorial

Membrane transporters enable substances to cross impermeable cell membranes. Whilst they primarily transfer endogenous substances such as nutrients, they can also transfer exogenous substances such as toxic metals, pharmaceuticals, and other toxic substances.

Membrane transporters function similarly to shuttle buses in that they efficiently move substances from one area to another – some only offer one-way services ie they return empty ready for the next load, whilst others offer 2-way services ie the loads can be moved in either direction.

The US Food and Drug Administration is focused on reducing the incidence and prevalence of drug-drug interactions, and has published a list of 10 key transporters that are now required to be included in the drug discovery process – being OCT2, OAT1/3, MATE1/2, OATP1B1/3, BCRP, P-gp (MDR1), MRP.

Confusingly, each transporter seems to have at least 3 different names by which it is known and the names are used interchangeably – for example P-gp is also known as MDR1, and is also identified as ATP-binding cassette sub-family B member 1.

The transporters can also change names as scenarios change – for example ThTr2 (Thiamine Transporter 2) was initially thought to be a thiamine-specific transporter, however, as there is now confirmation that it also transports choline and pyridoxine a name change is likely.

A range of substances can also inhibit transporter function with the primary mechanisms of action being -

i. **competitive inhibition** – direct competition for the transporter, and is often dependent upon which substance is there first, or which has greater numbers,
ii. **non-competitive inhibition** – may bind to another binding area or alternatively adjust to a slightly different docking site,
iii. **mixed-type inhibition** – a combination of both eg metallo-drugs can both competitively inhibit with their pharmaceutical and non-competitively with their metal or vice versa.

Inhibition mechanisms include trans-inhibition (intracellular) and cis-inhibition (extracellular) and may have variable impacts on the degree of inhibition.

Transporters can have several polymorphisms (variants), and seemingly it is becoming more important to know which polymorphism is present.

OCT1 polymorphism (variant)	% thiamine uptake compared to control
1.1	control
1.2	50
1.3	6
1.4	6
1.5	Equal to control
1.6	Equal to control
1.7	111
1.8	132

These are some of issues for which answers would be useful in for guiding our decision-making. What determines -

- which transporter route will be utilised by a substrate ie will it take the express or the scenic route?
- where the substrate disembarks eg kidney or hair follicle in the cochlear?
- the impact of many toxic metals on transporter availability and functionality? Toxic metals are commonly stored in bone, and as bone is constantly being remodelled so there is a constant release and uptake of toxic metals and consequently there are always toxic metals available to be substrates and to inhibit relevant transporters;
- expression of the epigenetic factors that influence transporter function?

These are some of the issues for which answers are required for guiding our decision-making -

- what is the turnaround time for the transporter ie how long does it take to go from Point A (pickup) to Point B (dropoff) and return to Point A? Is it minutes, hours, or days?
- what is the duration of inhibition of a transporter? Is the duration a similar period for all endogenous substances?

- if a pharmaceutical is only administered weekly eg methotrexate, then what is the duration of inhibition on the relevant (folic acid) transporters? If the relevant (folic acid) transporters are inhibited for days and not for hours, then does that mean the nutrient (folic acid) supplements administered during the period of inhibition are actually not being effective ie not entering and/or not departing relevant cells and organs? If blood tests show low, normal, high-normal or elevated levels is that directly because of the supplement or because of transporter inhibition?
- do transporters have different segregated areas to accommodate a range of substances so that inhibition by one substance may only close that segregated area and not inhibit the transporter carrying substances in other segregated areas? For example, can a pharmaceutical inhibit one part of a transporter and nutrients and/or toxic metals still be transported if they are carried elsewhere on the transporter?
- what are the factors that determine whether a drug becomes a substrate or an inhibitor?
- what is the impact on the gut microbiota? How much do they change the populations and therefore the range of nutrients produced and/or the amount of each nutrient available as a consequence of those changes in population?

Doctors and pharmacists do not learn about nutrition and therefore they cannot be expected to immediately accommodate negative nutrient impacts or even factor them into their management strategies. Every single prescribed medicine that negatively impacts a nutrient in some way is profoundly altering metabolic processes and not necessarily in positive ways. In fact, in many cases they can lead to ongoing negative health outcomes.

Ultimately, therapeutic substances regulators, globally, need to be regulating the inclusion of nutrient impact as part of the drug discovery process and that appropriate management strategies be recommended.

Many nutrients are still deemed to be transferred by “passive diffusion” – is that code for “We haven’t identified the relevant transporters yet” and does it mean and “we’re not really looking for them”?

When you review a person’s blood test results –

- do you then check whether any of the prescribed medicines interfere with nutrient transport?

- do you check the time of day the blood test was taken, and the times they consume their prescribed medicines?
- if the people you see are in concentrated industrial areas or near mining sites, do you question toxic metal interference?

Conclusions

Membrane transporters are key physiological agents, and interference with their operations has significant negative physiological, including nutritional, impacts. Seemingly our application knowledge is not keeping pace with the research evidence.

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: Huntingtons, gastritis, GORD

Biochemistry with Pharmaconutritional Consequences

Na:	143	mmol/l	Hb:	138	g/L	Albumin:	42	g/L	BSL:		mmol/l
K:	4.4	mmol/l	Lymph:	1.5		Total Protein:	68	g/L	HbA1C:		
Urea:	5.2	mmol/l	MCV:	90	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.059	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:		mIU/L

Other: eGFR > 90, CRP 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
EFEXOR XR		☐	NV	CD	↕	↓	☑				☑	☐	☐
MAXOLON		☐	N	D			☐				☐	☐	☐
Omeprazole	(20 mg/day) B1, B12, Ca, Fe,	☑	NV	CD	↑		☑				☑	☐	☐
OSTELIN	(1/day)	☐					☐				☐	☐	☐
Oxazepam		☑	N				☐		↕		☐	☐	☐
SERENACE	B2, folate	☑	NV	CD	↓	↕	☐		↑		☑	☐	☐
Temazepam		☑	NV	C			☑		↕		☑	☐	☐
Tetrabenazine		☐	N	CD	↑	↓	☐				☑	☑	☐

Transporter-mediated interactions and nutrients

DRUG	OCT1		OCT2		OCT3	
	B1, choline		B1, choline		B1, choline, carnitine	
	Substrate	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor
Maxolon	Y		Y	Y		
Omeprazole		Y		Y		Y
Oxazepam			Y			
Serenace	Y	Y				

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

Data summary

Biochemistry

Relatively recent biochemistry within acceptable ranges. Advisable to check plasma proteins (albumin, total proteins) as they are the primary transporters for four of the prescribed drugs and hypoproteinaemia may alter their effects and side effects.

Glycaemia

Currently prescribed 2 medications that alter glycaemia, being metoclopramide and Serenace.

Pharmaconutrition

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

Currently prescribed 4 medications that include vomiting, constipation, diarrhoea and dry mouth as side effects.

Currently prescribed 3 medications that include hyponatraemia as a side effect.

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

Currently prescribed ostelin (1/day). Advisable to check vitamin D levels and if still low then review current vitamin D management strategy.

There is increasing evidence that proton pump inhibitors such as omeprazole 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 magnesium status.

Bowel management

No regular interventions prescribed,

No PRN interventions prescribed,

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mrs AGT has a variable food intake and that now she is fully assisted with her meals.

Observations

Mrs AGT is a small rubinesque lady who was sitting in the Day Room when I went to speak to her - she told me she eats 3 meals and 3 snacks every day and has lots to drink, and that historically she vomited but does not these days.

Mrs AGT has remained weight stable for the last 18 months.

Pharmaconutrition assessment

Mrs AGT has been prescribed a proton pump inhibitor since admission 18 months 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 or famotidine (there is a general belief that they cause less nutritional harm than proton pump inhibitors).

Mrs AGT's diagnoses include falls - nutritional factors that may be useful to consider in falls management include -

- low calcium - more likely to be low if potassium or magnesium low; important in muscle function, currently prescribed omeprazole; it is difficult to clarify status as bones act as a reservoir to maintain blood calcium levels within a tight range;

- vitamin D – associated with muscle weakness and consequently falls; currently prescribed an intervention therefore advisable to clarify vitamin D status;

- low B12 - is important in the righting reflex when a person stumbles; prescribed omeprazole and Serenace therefore advisable to clarify status and if low then intervention recommended;

- low iron – currently prescribed omeprazole therefore advisable to clarify the status of iron and ferritin;

- low zinc – can decrease food intake through altered sense of taste and poor appetite, and consequently reduced muscle mass; currently prescribed omeprazole therefore advisable to clarify status;

- low magnesium - magnesium is important in vitamin D activation and muscle function, amongst other functions. Also currently prescribed omeprazole which significantly decreases magnesium absorption. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status Advisable to clarify magnesium status.

Mrs AGT's diagnoses include incontinence - nutritional factors that may be useful to consider in incontinence management include -

- low B12 – important in the righting reflex and currently prescribed omeprazole and Serenace therefore advisable to clarify B12 status.

Mrs AGT's diagnoses include Huntington's disease (HD) - nutritional factors that may be useful to consider include -

Ostelin – vitamin D is important in the maturation of OPCs to oligodendrocytes. This a useful intervention but may be inadequate to meet neuronal requirements therefore advisable to monitor status on a regular basis;

Serenace – decreases availability of folic acid which is important in oxidative phosphorylation (energy production) and also decreases availability of riboflavin which is the rate-limiting nutrient in one-carbon metabolism, therefore advisable to status of each of these nutrients on a regular basis ie at least annually;

Omeprazole – has a profound effect on neurological function as exampled -

- magnesium - decreases absorption therefore there is reduced activation of thiamine, vitamin D, vitamin C and iodide,

- vitamin C - decreases availability. 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. Further, in HD there are fewer SVCT2's (Sodium Vitamin C Transporter 2) and many of them are deformed so it is really difficult for vitamin C to enter many cells, especially neuronal and consequently the oxidative stress magnifies and thus hastens cell destruction;

- thiamine – decreases availability. Thiamine is important in astrocyte function – astrocytes are the intermediaries that provide all the substances essential for astrocytes to survive and thrive, and they also remove the garbage. Inadequate thiamine means damaged and dying astrocytes which causes pain;

- vitamin B12 – decreases absorption. B12 is important in oligodendrocyte and astrocyte function

- inhibits BCRP – inhibits riboflavin availability as it is a substrate for BCRP; BCRP has an essential role in the maintenance of cellular folic acid homeostasis. Advisable to monitor riboflavin and folic acid status on a regular basis.

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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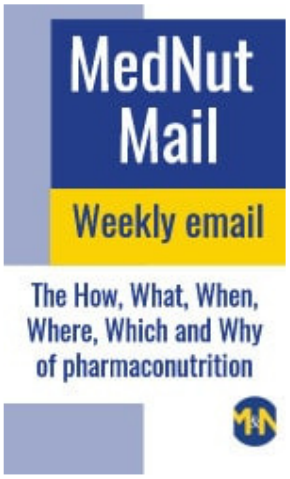

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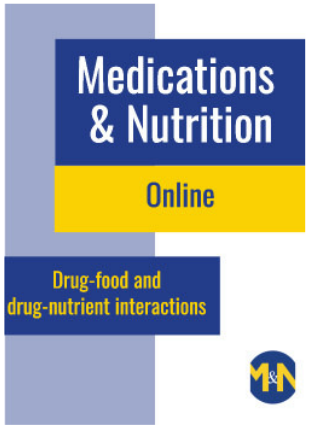

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