MedNut Mail

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

Excipients (ingredients) and pharmaconutrition

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Editorial

Excipients are the ingredients that comprise about 90% of a medicine - they are added to optimise some aspect of the medicine's administration and/or therapeutic benefit. Excipients seem to have 3 key roles, being -

1. to negatively impact pathophysiology (injury- or disease-caused upset physiological processes),
2. starting points for drug discovery projects,
3. treatment enhancers as functional supplements.

Functional roles of excipients include -

- **increasing** - absorption, biodegradability, buffering capacity, permeability, stability, solubility, swellability, viscosity, shelf life, patient compliance;
- **adding** - bulk, nutrients, antioxidants, flavours, colours;
- **enhancing** - binding capacity, disintegration capacity, dispersion capacity, pH adjustment, safety and effectiveness during storage and/or use;
- **assisting** - in product identification.

Sometimes a substance can be an excipient in one medicine and the active ingredient in another – a common example is vitamins.

Perceived safety

Partly because of their overlap with both the food industry and the cosmetics sector there has been a long-standing perception that excipients are either inert or have limited biological activity (of biological origin applied therapeutically). However, this is now being challenged as evidence suggests that excipients are more bioactive (alter physiological processes) than assumed, and can potentially alter drug effectiveness, biological functions, and physiological response. For example, excipients have been found to alter factors such as gastrointestinal transit time, their interactions with gut microbiota, enterocyte permeability, transporter activity (including BCRP, P-gp, OATP2B1). Further and importantly, compatibility of excipients with other excipients, and the potential for excipient toxicity and harm are steadily gaining attention.

Many excipients have been grandfathered into acceptance by GRAS (Generally Regarded As Safe) – an FDA Act underpinned by expert opinion of their safety based on long-term useage. Consequently, excipients have not had their safety profiles

actively tested. Machine learning and increased awareness of potential harm may address some of this oversight.

Positive impacts

Whilst there is considerable concern about excipient-induced negative impacts, excipients can also be manipulated to confer positive impacts, and an increasing number of medicines are being developed that utilize excipients to enhance or increase therapeutic benefit.

Negative impacts

In general, negative impacts are not classified according to source ie whether it is due to the therapeutic ingredient or an excipient. Consequently, avoidance of a concerning substance becomes very difficult.

There are no regulatory requirements for inclusion of excipients' concentrations in the Product Information document – albeit some regulatory authorities such as the EMA (European Medicines Agency) do now require the quantity of specified substances such as lactose, to be included.

Given their extensive useage, varying concentrations, and ability to alter some membrane transporters' functions, it is becoming increasingly important for clinicians to be aware of the concentrations of the various excipients, their potential to cause or exacerbate negative impacts, and how those negative impacts manifest.

Further, clinicians need to know whether the excipients -

- are known or likely allergens. The non-identification of a potential allergen means extreme risk of harm – especially as the sensitivity of some people can be such that it is a presence or absence issue;
- are likely "intolerancers" (compounds generating an individual response). As many intolerances have thresholds it is essential for clinicians to be aware of individual excipient quantities in order to address individual thresholds and to modify intake in accordance with those threshold levels;
- have multiple names and what they are in order to ensure clarity of intake. Examples - there are multiple terms applied for gluten inclusion, and many clinicians do not realise galactose is present in lactose. A global standard for excipient terminology would minimise both consumer and health professional confusion.

The negative impacts of excipients can be both –

1. **short term** - are relatively immediate such as diarrhoea, urticaria, etc,
2. **long term** - are much more insidious. For example, a young child behaving badly as a consequence of (especially frequent) exposure to their excipient intolerance is likely to gain a reputation for difficult behaviours that will limit their experiences in relation to schooling, socialisation, and other opportunities, and ultimately, potential failure to achieve their full potential.

How many adverse reactions currently attributed to the medicine are excipient-induced and not due to the therapeutic substance?

Potential cumulative effect

The drug discovery process is conducted in isolation however prescribed medicines are not typically administered and consumed in isolation – some common examples are metformin + proton pump inhibitor, and a proton pump inhibitor + furosemide + digoxin. Further it is not unusual for some groups (eg Aged Care, Disability, Mental Health) to be prescribed many different medicines that are commonly administered at similar times. Working in Aged Care I commonly saw many residents prescribed a dozen or more different medicines, and their dosages may have required several tabs or caps administered on multiple occasions throughout the day; the maximum number of different medicines prescribed to one person whom I saw, was 24.

Prescription of multiple different medicines, commonly administered at similar times means there is a high risk of a cumulative effect of excipients. The presence of a tiny amount of an excipient in one medicine may not be “clinically significant” but if administered several times per day and/or with multiple other medicines containing the same excipient(s), then the initial tiny amount is likely to increase to an amount that has the potential to cause harm.

Given the commonality of excipients across 3 sectors (pharmaceutical, food, cosmetics) then useful information would include their individual quantities in each product in each of the sectors. There is an assumption that most people eat well however this is not supported by the supermarket consumption lists that highlight a strong trend to increasingly processed foods – the more highly processed the food the greater the excipient presence. The concept that cosmetics may be altering our health and/or nutritional health is quite foreign and needs to be addressed.

Clinical implications

From a nutrition perspective, excipients fall into 3 main groups -

1. **medical** – intolerances due to the presence of gluten, lactose, galactose, phenylalanine, salt, specific flavours, specific colours (why are so many

medicines for children coloured red – the combination of sick child and red medicines must be a nightmare);

2. **religious** – exclusions include beef, pork, seafood, etc;
3. **philosophical** – vegetarian, vegan, ketone, fruitarian, etc.

So that appropriate nutrition interventions can be initiated without compromising the therapeutic benefit of the medicine from a pharmaconutrition perspective, we need to know -

- the negative impact profile of each excipient and preferably their mechanisms of action,
- the "per 1 mL" volume - the minimum mass, the maximum mass and the average mass,
- whether there will be, directly or indirectly, an alteration to food intake and/or nutrient availability and/or food choice.

The nutrition support product sector has a global standard that their products not contain gluten or lactose - perhaps the pharmaceutical sector could emulate this practice and make it a global standard for their sector as well.

A really informative paper on this topic - Biologic excipients: Importance of clinical awareness of inactive ingredients. https://doi.org/10.1371/journal.pone.0235076.

Clinical Questions

What actions will you initiate as you review the nutritional implications of someone's prescribed medicines, will you –

- check for medical, religious and philosophical compliance?
- write to the TGA, FDA and EMA and request that the mini-max and average concentrations, and negative impacts of each excipient be included in the Product Information documents?
- advise the likely mal-nutrition as a consequence of an excipient-nutrient interaction via the transporter network at the weekly Team Meeting (this is likely to be difficult given the early stage of this research)?

Conclusions

Excipients are important in many aspects of the development, manufacture and consumption of medicines however they are steadily gaining attention as the range and extent of their biological activity becomes apparent.

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: delirium

Other: GORD, deafness, subclinical hypothyroidism

Biochemistry with Pharmaconutrition Consequences

Na:	128	mmol/l	Hb:	144	g/L	Albumin:	41	g/L	BSL:		mmol/l
K:	4.8	mmol/l	Lymph:	0.9		Total Protein:	75	g/L	HbA1C:		
Urea:	4.8	mmol/l	MCV:	93	mmol/l	B12:		pmol/L	INR:		
Creatinine:	0.055	mmol/l	Zn:		umol/l	Folate:		nmol/L	TSH:	3.90	mIU/L

Other: eGFR > 60, CRP < 5, T4 13, T3 3.7, vit D 105, Ca 2.42, Ca corr 2.45, phos 1.16, Mg 0.89

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
Esomeprazole	(20 mg/day) B1, B12, Ca, Fe,		☑	NV	CD	↑		☑				☑	☐	☐
EUTROXSIG	(50 mcg/day) A, Ca, carnitine,		☑	V	D	↓		☐				☐	☐	☑
MIRTAZON			☐	N	D	↑	↑	☐				☑	☐	☐
Paracetamol			☐	NV	CD			☐				☐	☐	☐
VITA-D GEL CAPS	(1000IU/day)		☐					☐				☐	☐	☐

Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OAT1	
Nutrients - Substrates	B1, choline, carnitine		B1, choline, NMN, carnitine,		B1	
DRUG	Sub	Inh	Sub	Inh	Sub	Inh
esomeprazole		Y				
eutroxsig						
mirtazon				Y		
Paracetamol						Y
cholecalciferol						

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

Data summary

Biochemistry

Recent relevant biochemistry indicates -

- low sodium - associated with increased risk of falls, and poor appetite. Hyponatraemia can be due to many causes including SSRI intervention, therefore advisable to recheck sodium status and if low then include reviewing mirtazon intervention;

- elevated normal TSH – advisable to review eutroxsig intervention.

Glycaemia

Currently prescribed 1 medication that alters glycaemia.

Pharmaconutrition

Currently prescribed 4 medications that include diarrhoea as a side effect.

Currently prescribed 3 medications that include nausea and vomiting as side effects.

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

Eutroxsig + adjunct carnitine (2 mg/day or 4 mg/day) is effective in decreasing symptoms of hyperthyroidism.

Regular monitoring sodium levels recommended whilst mirtazon prescribed.

Currently prescribed vitamin D (1 tab/day). Advisable to recheck status as current results 6 months old.

There is increasing evidence that proton pump inhibitors such as esomeprazole 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. Current magnesium levels within acceptable range however advisable to monitor status on a regular basis.

Bowel management

No regular interventions prescribed.

Oral PRN aperient prescribed.

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mrs ACM eats well, but not quite as well as historically.

Observations

Mrs ACM is a charming European lady with thyroidy eyes and who was sitting in the Day Room when I went to speak to her - she told me she speaks five languages - Italian, Hungarian, German, French and English! Mrs ACM told me she eats well, that the food is lovely and that she has disturbed sleep

Mrs ACM has been losing weight for the last year.

Pharmaconutrition comments

Thyroxine dose is directly related to weight and change in weight status alters drug effectiveness therefore since Mrs ACM has lost about 8 kg within the last year she is at risk of over-medication - advisable to check thyroid function.

Mrs ACM has been prescribed a proton pump inhibitor since admission (4 years ago) and likely before then. There is increasing evidence that longterm (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).

Low B12 associated with increased TNF-α response and demyelination; TNF-α is a key marker of the inflammatory response. B12 deficiency manifests as weakness, light-headedness, vertigo, tinnitus, palpitations, angina, sore tongue, anorexia, moderate weight loss, diarrhoea, demyelination, axonal degeneration, parasthesias, unsteady gait, limb stiffness and weakness, irritability, apathy, somnolence, emotional instability, marked confusional or depressive states; visual impairment. Currently prescribed esomeprazole therefore advisable to check B12 status and commence interventions if low.

If Mrs ACM's weight loss is due to overmedication with eutroxsig then this should resolve as the dose is adjusted. However if weight loss is due to inadequate food intake then advisable to check zinc levels as zinc is important in sense of taste and release of the hunger hormone Neuropeptide Y; she has been prescribed a proton pump inhibitor since at least admission and PPIs are associated with reduced zinc absorption.

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

- loss of weight – currently prescribed 4 drugs with direct and indirect side effects that negatively impact food intake;

- low calcium - more likely to be low if potassium or magnesium low; important in muscle function, currently prescribed esomeprazole therefore advisable to monitor status;

- low B12 - is important in the righting reflex when a person stumbles; prescribed esomeprazole therefore advisable to monitor status;

- low iron – important in haemoglobin formation, currently prescribed esomeprazole therefore advisable to monitor status;

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

- low magnesium - magnesium is important in activation of vitamin D, B12, vitamin C, iodide, and muscle function, amongst other functions. Also currently prescribed esomeprazole which significantly decreases magnesium absorption. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status Advisable to monitor magnesium status;

- low carnitine - carnitine is both absorbed and produced de novo, and is important in a range of muscle functions; eutroxsig increases carnitine excretion; magnesium is important in de novo carnitine production. Advisable to clarify status.

Mrs ACM'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 and folic acid levels and if low then interventions recommended;

- vitamin C - inadequate dietary intake associated with deafness. Currently prescribed esomeprazole which reduces conversion of vitamin C to its active form;

- 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.

Nutrients important in bone health include –

- Cobalamin (B12) – is important in osteoblast activity, and bone strength. Currently prescribed esomeprazole therefore advisable to check B12 status and if low then intervention recommended;

- Folate (B9) – is important in osteoclast activity, and in bone mineral density. Currently prescribed esomeprazole therefore advisable to check folic acid status and if low then intervention recommended;

- 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 esomeprazole therefore advisable to monitor vitamin C status and if low then intervention recommended;

- Calcium – is important in skeletal development and growth, and bone mineralization. Currently prescribed esomeprazole therefore advisable to monitor calcium status and if low then intervention recommended;

- 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 esomeprazole therefore advisable to monitor magnesium status and if low then intervention recommended;

- Zinc – is important as a cofactor for many metalloproteins involved in bone development. Currently prescribed esomeprazole therefore advisable to monitor zinc status and if low then intervention recommended;

- Carnitine – is important in intracellular calcium signalling, in stimulating human osteoblast functions, activity, differentiation and proliferation, in increasing expression of collagen type 1, bone sialoproteins, osteocalcin and osteopontin, as an antioxidant and protects against oxidative stress, modulates mitochondrial activity in osteoblasts, and by likely supporting fulfillment of the high metabolic demand of osteoblasts during bone formation. Currently prescribed eutroxsig therefore advisable to monitor carnitine status and if low then intervention recommended.

What else would you include?

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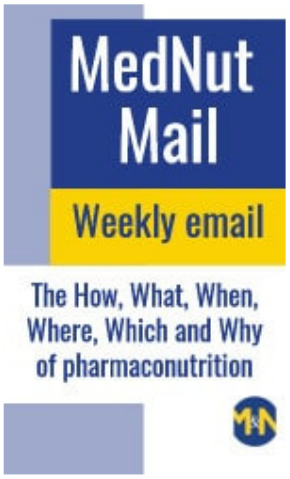

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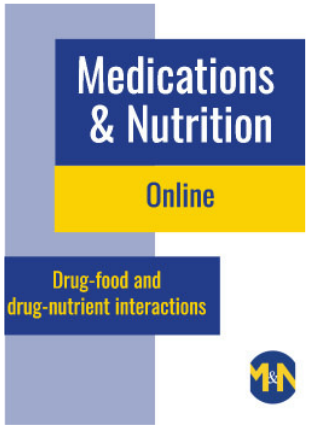

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