MedNut Mail

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

Toxic metals and drug transporters – is there a concern?

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https://medicationsandnutrition.online

Commentary

Transporters are euphemistically called “drug transporters” however their primary role is to move physiological substances to sites requiring their presence. There is a lot of drug company interest in transporters for 2 reasons, being

- US FDA now requires this information to be included in drug discovery submissions, and
- drug companies consider they may be the vehicles to provide access to the bits of the body they (drugs) currently can’t currently access, or find it difficult to access such as crossing the blood-brain barrier.

Transporters have 3 mechanisms of action, being -

- **Inducer** – enhances the effectiveness of the substance being transported. A well-known example is grapefruit juice and cytochrome P450 isoform 3A4 whereby grapefruit increases the effectiveness of some drugs such as felodipine/nifedipine;

- **Inhibitor** – blocks the effectiveness of the transporter for a period of time – seemingly typically about 1 hour. For example, metformin inhibits THTR2 (Thiamine Transporter 2) ie the transporter of thiamine from the intestines;

- **Substrate** – can be carried by the substance. For example, metformin is a substrate for OCT 2 (Organic Cation Transporter 2) which transports thiamine to the kidneys.

Toxic metals have a capacity for molecular mimicry and can be carried by the same transporters as nutrients however are not regulated by physiological processes in the same way as the essential elements and therefore can cause harm. It also means that once absorbed, toxic metals can be transported throughout the body to many of the same sites available to the essential elements.

Examples of “shared” transporters include -

- arsenic can travel on glucose transporters, water channels, thiamine and phosphate transporters;
- cadmium (Cd) can be transported on thiamine, zinc, iron, magnesium and calcium transporters, and albumin;
- lead can travel on calcium and zinc transporters;
- mercury can be transported by albumin, homocysteine, and a range of other substances, inhibits aquaporins (water channels), and is a substrate for some transporters.

What makes many of the toxic metals even more harmful is that they are stored in the body in organs such as the liver and bone. Using bone as an example, continuous bone remodelling means the bone is constantly releasing and taking up toxic metals.

A hidden form of harm is the competition between toxic metals, prescribed medicines and nutritional factors for access to relevant transporters, and seemingly it all depends upon which one gets to the transporter first. Using thiamine, metformin and cadmium as an example:

- **thiamine** is typically absorbed during the meal, and so if there is no competition, will be first on the transporter,

- **metformin** is a substrate for many of the thiamine transporters, and is typically administered before meals therefore is likely to have first access to the transporters and so will fill the transporter slots and therefore the thiamine in that meal will not be transported,

- **cadmium** is also a substrate for some of the thiamine transporters, is typically in a state of flux ie being released and taken up by various body processes, and is therefore more likely to be available to fill the transporter slots first and so neither metformin nor thiamine will be transported. In this example the long term consequences are altered therapeutic benefit from the metformin and hidden malnutrition due to sustained chronic inadequate thiamine uptake.

The utilisation of transporters by toxic metals via molecular mimicry is in the early stages of research, however the early findings are pointing to areas of harm not previously considered ie the alteration to therapeutic benefits conferred by prescribed medicines, and the mal-nutrition impacts.

Do you consider environmental impacts in your daily clinical practice?

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: epilepsy, cerebral palsy

Biochemistry with Pharmaconutritional Consequences

Na:	140	mmol/l	Hb:	148	g/L	Albumin:	38	g/L	BSL:		mmol/l
K:	4.6	mmol/l	Lymph:	2.8		Total Protein:	67	g/L	HbA1C:		
Urea:	4.0	mmol/l	MCV:	93	mmol/l	B12:	757	pmol/L	INR:		
Creatinine:	0.048	mmol/l	Zn:		umol/l	Folate:	11.6	nmol/L	TSH:	1.72	mIU/L

Other: TRF 2.3, satn 52%, ferritin 21, chol 5.8, Tg 0.9, HDL 1.4, LDL 4.0, Non-HDL 4.4, Chol:HDL 4.1, Ca 2.38, Ca corr 2.42, v

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
BISALAX	enema - PRN	☐	N	CD			☐				☐	☐	☐
Cholecalciferol	(4000 IU/day)	☐					☐				☐	☐	☐
EPILIM	EC - B12, B6, biotin, Ca, carnit	☑	NV	CD	↑	↕	☐				☐	☐	☑
FERROGRAD C	MR - Zn	☐					☐				☐	☐	☐
KEPPRA	D	☐	NV	D	↑	↑	☐				☑	☐	☐
Lactulose		☐	NV	D		↓	☐				☐	☐	☑
LAMICTAL	carnitine, D	☐	NV	D		↓	☐				☐	☐	☐
Sertraline	Na	☑	NV	CD	↑	↑	☐				☑	☐	☐
TEGRETOL	CR - B6, biotin, carnitine, D, fo	☐	NV	CD	↑	↑	☑				☑	☐	☐

Extra drug:

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

Although recent relevant biochemistry indicates markers of concern, none seem to be related to the currently prescribed medicines.

There is some evidence that concurrent administration of magnesium with epilim (Sodium valproate) enhances epilim's anticonvulsant effect.

Ferrograd+C (Ferrous sulfate + ascorbic acid) comprises ferrous sulfate + vitamin C. Iron is available in two forms being ferrous and ferric - ferrous is the absorbable form whilst ferric requires vitamin C to convert it to ferrous in order to be absorbed. The combination of iron in a ferrous form plus vitamin C is unnecessary and implies the drug company is being disingenuous. Ferrograd+C has a very slow rate of dissolution and poor rate of absorption ie less than 30%. Both ferrous sulfate and ferrous fumarate have rapid rates of dissolution and higher rates of absorption. Advisable to review iron intervention and consider alternative, more effective products as outlined.

Chronic use of lactulose may decrease water and electrolytes, especially potassium, and their regular monitoring recommended.

At increased risk of thiamine deficiency as lamictal (lamotrigine) is both an inhibitor and substrate for some of the thiamine transporters therefore advisable to consider a thiamine intervention. Advisable to administer thiamine intervention at a time when none of the inhibitors and substrates are administered. Very early evidence indicates nutrient interventions are effective if administered either one hour before or two hours after drug administration.

If a thiamine intervention is initiated then advisable to consider a magnesium intervention (to provide ~ 300 mg elemental magnesium/day) as adequate magnesium status is essential for activation of thiamine, vitamin D and iodine.

Regular monitoring sodium levels recommended whilst sertraline prescribed as there is increased risk of hyponatraemia - hyponatraemia is associated with increased risk of falls and poor appetite.

Mr AAP is at increased risk of diabetes as a consequence of some of his prescribed medicines include altered glycaemia as a side effect in conjunction with likely dysfunctional mitochondria.

What else would you include?

Toxic metals and drug transporters – is there a concern?

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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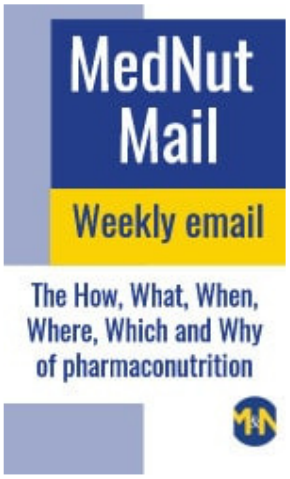

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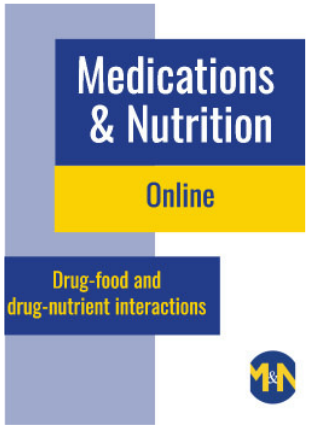

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