MedNut Mail

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

MATE1/2 and pharmaconutrition

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Editorial

Multi drug and toxin exclusion transporters (MATE1) and (MATE2) are major efflux transporters involved in the hepatic and renal excretion of many cationic endogenous and xenobiotic substances. As efflux transporters they primarily move lipophobic substances -

- out of the liver ie hepatic biliary excretion – MATE1,
- out of the kidneys and into urine ie renal excretion – MATE1/2.

Confusingly there are a number of MATEs, being -

1. MATE1 - mediates the efflux of diverse substrates, primarily organic cations, in the kidney and the liver;
2. MATE2 - is not functionally expressed in classic *in vitro* transporter systems, and so two splice variants were developed, being -
   a) MATE2-K - the preferred model for assessing MATE2 modulation in *in vitro* systems;
   b) MATE2-B - a non-functional transporter.

MATE1

MATE1 transports various organic cations, some noncharged compounds (some drugs such as gabapentin lactam), and some zwitterions (neutral molecules that have both positive and negative charge), and some organic anions.

MATE1 is expressed in the liver at the apical bile canalicular membrane of hepatocytes, in the kidney at the apical side of renal proximal and distal tubule cells, in other tissues including skeletal muscle, adrenal gland, testes, and heart.

Nutrient substrates include thiamine, and creatinine.

MATE2/2-K

MATE2/2-K is a polyspecific transporter of organic cations, zwitterions, noncharged compounds, and anion molecules.

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MATE2 is exclusively expressed in the brush border (apical, urine side) membrane of proximal tubular cells.

Nutrient substrates include thiamine, carnitine, creatinine, and N-methylnicotinamide (NMN).

MATE deficiencies can be long term or short term, and are likely due to -

1. **Polymorphisms (variants)** – variations of a specific DNA sequence that can involve either a single nucleotide (aka single-nucleotide polymorphism, or SNP), or a longer DNA sequence.

   Genetic polymorphisms in the efflux transporters are known to influence both the biochemical and physiologic effects of many of their substrates resulting in either hyper-functioning ('gain-of-function') or hypo-functioning ('loss-of-function') of the relevant efflux transporter with consequent altered responses.

   Polymorphisms are acknowledged for MATEs1/2.

2. **Environmental** – many xenobiotics including environmental compounds, are known to interact with membrane transporters and the mechanisms of the interactions are likely to include stimulation, partial inhibition and/or interference with transporter-mediated signalling with outcomes such as unanticipated drug interactions and physiological -disruptions resulting in developmental defects. Examples include -
   a. Inhibition of inhibition of MATE1 will result in cardiac accumulation of dofetilide with resultant negative consequences;
   b. OCT and MATE transporters appear to work in tandem when moving organic cations as OCTs clear them from the bloodstream - MATE1 from the liver and MATE1/2-K from the kidney. Some xenobiotics such as cadmium and candesartan, have been found to create a divergence in the regulation of the tandem transporters, and the proposed mechanism of action is based on these xenobiotics (cadmium and candesartan) both being OCT substrates and MATE inhibitors. The consequence is an accumulation of substrates in the liver and/or kidney due to delayed excretion.

The defined specific and sensitive biomarker for identifying MATE-mediated drug-drug interactions in the kidneys is NMNCL-R, but not its circulating levels.

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What actions will you initiate when you see someone whose prescribed medicines alter MATE function, will you –

- clarify adequacy of dietary intake of thiamine, carnitine and niacin, request blood tests, and then compare findings?
- If there is disagreement between oral intake and blood test results, will you question inhibition of the transporters?
- recommend nutrient interventions be administered at different times from the prescribed medicines?

Conclusions

MATE transporters are particularly important in hepatic and renal excretion, and disruption to their function has many negative impacts

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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: PPM, myasthenia gravis, hypercholesterolaemia

Biochemistry with Pharmaconutrition Consequences

No recent relevant results available.

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
Atorvastatin		☑		NV	CD	↑	↓	☑				☐	☐	☐
Citalopram	Na	☐		NV	CD	↑	↕	☑		↑		☑	☑	☑
Esomeprazole	(40 mg/day) B1, B12, Ca, Fe,	☑		NV	CD	↑		☑				☑	☐	☐
FERRO-F	Ca, Mg, Zn	☐						☐				☐	☐	☐
Indapamide	Ca	☑		NV	CD		↓	☐				☑	☐	☑
MOVICOL		☐		N	D			☐				☐	☐	☐
OSTELIN	(2/day)	☐						☐				☐	☐	☐
PANADOL OSTEO		☐		NV	CD			☐				☐	☐	☐
PLAVIX		☑		N	CD	↓		☑				☐	☐	☐
Prednisolone	Ca, Cr, D, Iodine	☑		NV	CD	↕	↑	☐				☐	☐	☑
Pyridostigmine		☐		NV	D			☐				☐	☐	☐
TARGIN		☐		NV	CD		↕	☑				☑	☑	☐

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Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OCT3		OCT6		OCTN1		OCTN2		MATE1/2	
Nutrients - Sub	B1, choline, carnitine		B1, choline, creatinine		B1		carnitine		carnitine		carnitine		B1, creatinine	
Nutrients - Inh														
Location	intestines, liver		kidney		intestines, liver, kidney		testis, endometria		Intestines, kidney		Intestines, liver, kidney		kidney	
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Citalopram		Y		Y	S									
Esomeprazole		Y												
Clopidogrel		Y		Y										
Prednisolone				Y										
Targin				Y										

Sub – substrate, Inh – inhibitor, B1 - thiamine

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

Data summary

Biochemistry

No recent relevant biochemistry available. Advisable to check plasma proteins (albumin, total proteins) as markers of nutritional status. The plasma proteins are the primary transporters for six of the prescribed drugs and hypoproteinaemia may alter their effects.

Glycaemia

Currently prescribed 7 medications that alter glycaemia, being amlodipine, aspirin, atorvastatin, metformin, paracetamol, quetiapine, targin.

BSLs - tested monthly
- advisable to check HbA1c and clarify overall glycaemic control.

Diabetes drugs
- metformin has a duration of 12 hours.

Diabetes drugs coverage
- before breakfast BSLs - minimal, if any, coverage from previous evening's metformin;
- before evening meal BSLs - no coverage from previous evening's metformin.

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Pharmaconutrition

Currently prescribed 3 medications that include anaemia, dysphagia, altered zinc status, altered iron status as side effects.

Currently prescribed 4 medications that include hyponatraemia, altered lipids, altered potassium, and sweating as side effects.

Currently prescribed 11 medications that include nausea and vomiting as side effects.

Currently prescribed 9 medications that include constipation and altered taste as side effects.

Currently prescribed 8 medications that include diarrhoea and dry mouth as side effects.

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

Currently prescribed 7 medications that include altered appetite as a side effect.

Currently prescribed 7 medications that include altered weight status as a side effect.

Amlodipine, esomperazole and irbesartan impair zinc status.

Vitamin C (960 mg/day) attenuates aspiring-induced gastric injury.

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

Metformin decreases B12, B1, B2, B6, B9 and magnesium absorption – advisable to monitor on a regular basis ie at least annually.

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

Dietary levels of caffeine intake in conjunction with paracetamol inhibit antinocieception.

Concurrent ingestion of paracetamol and iron resulted increased rate of iron absorption and decreased extent of drug absorption; the authors advise drug and iron to be administered at different times from each other.

Currently prescribed two drugs that decrease B12 absorption - being metformin and esomeprazole, therefore advisable to check B12 levels and clarify current status.

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Statins interfere early in the cholesterol metabolic pathway and consequently decrease -

- conversion of sun to vitamin D - vitamin D intervention recommended;
- production of CoQ10 - important in cellular energy production; CoQ10 intervention recommended;
- DHEA production - low DHEA associated with increased risk of metabolic syndrome; intervention recommended.

Therefore, advisable to clarify cholesterol status.

Bowel management

No regular intervention prescribed.
No PRN interventions prescribed.
Nurse Initiated oral aperients administered 3 x Feb, 3 x Jan.

Staff comments

Staff advise improving appetite.

Observations

Mrs AGY is a small, pale, anxious, rubinesque lady who was asleep in bed and did not stir to her name when I went to speak to her.

Mrs AGY's current weight status is indeterminate.

Pharmaconutrition assessment

Earlier in the morning Mrs AGY had commented the food had an unacceptable taste at times. Zinc is important in sense of taste and release of the hunger hormone. Since Mrs AGY -

- has lost weight since admission and weight loss is associated with depletion of zinc status;
- is prescribed esomeprazole which decreases zinc availability;

advisable to check zinc status and if low then consider a short term (90-120 days) zinc intervention however its effectiveness is questionable whilst a proton pump inhibitor is prescribed.

Since Mrs AGY is pale, advisable to check iron levels and if low then short term (90-120 days) intervention recommended however evidence indicates iron deficiency anaemia is unlikely to resolve whilst a proton pump inhibitor is prescribed.

Mrs AGY has been prescribed a proton pump inhibitor for an indeterminate period.

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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).

Mrs AGY'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. 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 as currently prescribed esomeprazole which decreases conversion of vitamin C to its active form. Vitamin C is not considered part of the pain management armament however it won't cause harm and evidence suggests it may confer benefit.

- 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 and metformin therefore advisable to clarify B12 status.

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- 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 , metformin which decrease magnesium availability therefore advisable to clarify magnesium status.

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

- loss of weight – prescribed 12 drugs with side effects that negatively impact food intake;

- low potassium - important in muscle function, currently prescribed esomeprazole therefore advisable to clarify status;

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

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

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

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

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

What else would you include?

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