MedNut Mail

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

Methotrexate and folate – pharmaconutrition implications

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9th November 2021

https://medicationsandnutrition.online

Commentary

Methotrexate is both an antagonist and an analogue of folic acid ie it is a nutrient-derivative drug. Methotrexate was developed in the 1940s as an anticancer intervention, in 1951 it was trialled as a rheumatoid arthritis (RA) intervention, and in 1986 was licensed to be an RA therapy.

Methotrexate is a substrate (can be transported by the transporter) for the 3 key folate transporters, being proton-coupled folate transporter, reduced folate carrier and folate receptors.

Methotrexate is absorbed by the proton-coupled folate transporter in the jejunum, and is commonly transferred into the cells by reduced folate carrier, and folate receptors have a smaller role in absorption. Reduced folate carrier (RFC) facilitates some folate absorption from the colon. There are multiple other folate transporters however it is not clear whether methotrexate accesses those transporters.

Folic acid deficiency is the most prevalent vitamin deficiency globally which is surprising given its important role in one-carbon metabolism within the cytosolic and mitochondrial pathways; these pathways are also primary targets for drug interventions in the treatment of many diseases and especially cancers.

Effectiveness of methotrexate dose plateaus at doses above 15 mg/week, which suggests saturation of the intestinal transporters.

I have been unable to establish the folate dose required to saturate the folate transporters at the intestinal level, nor the degree of folate displacement caused by methotrexate.

The evidence seems to be increasing for a therapeutic range for folic acid ie sustained excessive folic acid levels are increasingly being associated with risks of harm, and particularly neurological harm.

Folate supplements prescribed as an adjunct to methotrexate most commonly provide 5 mg folate/day whilst some provide 1 mg folate/day.

Recommended daily folate intake for those aged 14+ years			
	mcg	mg	g
day	400	0.4	0.0004
week	2,800	2.8	0.0028

One paper compared high-dose folate (≥ 25 mg/week) with low-dose folate (≤ 10 mg/week) and found no statistical difference in methotrexate efficacy.

In other, unrelated papers whereby 2 different doses of a nutrient intervention administered with a drug resulted in no statistical difference in outcome it was because both nutrient doses flooded the intestinal transporters – I suggest it is likely the same with the folate dosing in the above referred-to paper.

However, given there is increasing concern that folate may have a therapeutic range, I suggest 5 mg folate doses are excessive and likely to be modified as the evidence increases; the 1 mg/day intervention seems more congruent with physiological requirements.

Optimal pH for proton-coupled folate transporter is 5.0-5.5 and as pH increases toward 7.0, transport decreases dramatically and is almost undetectable above 7.0. RFC transport activity falls with decreasing pH from pH 7.4 and is negligible below a pH of 6.0–6.5.

Since the proton-coupled folate transporter requires an acidic environment to be effective one can only wonder about the level of impact of concurrent proton pump inhibitor administration on the absorption and effectiveness of folate and methotrexate interventions.

So, when you see someone prescribed folic acid supplements +/- methotrexate will you integrate the following into your clinical assessments -

- check their folate status, and request it to be checked if it is not available?
- ensure the levels are not above the recommended upper limit?
- recommend reducing frequency of the intervention and/or the dose if the levels are at the high end of normal range or above range?

Conclusions

Methotrexate has been around for 70+ years and yet there are still arguments about whether its effectiveness is compromised with concurrent administration of folic acid, and we still don't know the degree of its negative impact on folate absorption and therefore the required intervention dose that confers benefit without harm.

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: SCC lower lip

Other: AF, GORD, pneumonia, hyponatraemia, chronic pain

Biochemistry with Pharmaconutritional Consequences

No recent relevant data 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
ACTILAX		☐		NV	D		↓	☐				☐	☐	☑
COLOXYL WITH S		☐			D			☐				☐	☐	☐
Metoprolol		☐		NV	CD	↑		☑				☑	☐	☑
MOTILIUM		☑		N	CD		↕	☐	↓			☑	☐	☐
MOVICOL		☐		N	D			☐				☐	☐	☐
SOMAC	(40 mg/day) B1, B12, Ca, Fe,	☑		NV	CD		↓	☑				☑	☐	☐
Warfarin	D	☑		NV	D			☑				☐	☐	☐
		▩						▩				▩	▩	▩

Extra drug: thiamine, norspan

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

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 3 of the prescribed drugs, being motilium, somac and warfarin, and hypoproteinaemia may alter their effects.

Chronic use of actilax and coloxyl + senna may promote excessive loss of water and electrolytes, especially potassium, and their regular monitoring recommended.

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

A proton pump inhibitor has been prescribed since admission (2016), and has probably significantly impaired 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.

Mrs AAQ has remained remarkably weight stable about 34 kg and staff advise she eats well.

Mrs AAQ is a small, pale, skinny lady with a lovely smile and who told us she eats well. When asked if she feels upset in the tummy she indicated she does sometimes feel upset in the tummy and remained fixated on her tummy for the rest of our conversation; when asked about pain she also pointed to and rubbed her tummy.

Since Mrs AAQ is pale, advisable to check iron levels and if low then short term (90-120 days) intervention recommended however effectiveness of an iron intervention is likely to be compromised due to proton pump inhibitor prescription. Strategies to increase iron intake include

- provision of foodstuffs such as pate, liver, salami, liverwurst; and/or

- concurrent administration of an iron tablet, with a probiotic to protect the beneficial gut microbiota.

Given Mrs AAQ is pale advisable to review 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),

- an iron infusion as it bypasses the gut and is a reasonable and effective alternative for improving iron status.

Thiamine activation requires an adequate availability of magnesium however a proton pump inhibitor is prescribed and therefore magnesium levels are at high risk of being compromised - advisable to clarify magnesium status. Women require 320 mg elemental magnesium per day, however as there are side effects if non-food magnesium of 350+ mg elemental magnesium is administered, advisable to consider a magnesium intervention that provides about 300 mg elemental magnesium per day.

Mrs AAQ has been prescribed a proton pump inhibitor since admission (2016) 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;

- increased risk of dementia;

- 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).

Given the duration of prescription of the proton pump inhibitor drug advisable to check B12 status. There is disagreement between pathology ranges and research findings with regard to appropriate B12 levels - neuro-imaging research shows a direct causal link between B12 status, damage to the brain, and consequent memory impairment; they also found increasing memory impairment as B12 levels dropped even whilst within currently defined acceptable ranges. The authors recommend B12

interventions once levels are less than 300 pmol/L.

Current diagnoses include hyponatraemia therefore advisable to check sodium levels and clarify current status.

Mrs AAQ's diagnoses include chronic pain - pharmaconutrition factors to consider include -

- 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 - the optimal intervention is 500 mg vitamin C/day (if more than 500 mg vitamin C administered at a time then the excess above 500 mg is not absorbed as the vitamin C transporters are overloaded). Vitamin C is not considered part of the pain management armament however it won't cause harm and evidence suggests it may confer benefit. Currently prescribed a proton pump inhibitor which decreases conversion of vitamin C to its active form.

- evidence indicates substantial relief of neuropathic pain by thiamine, pyridoxine and cyanocobalmin separately, and in combination there was a synergistic benefit; however prescribed somac which decreases thiamine availability and B12 absorption.

- vitamin K - has been found to suppress the inflammatory cytokines and NF-kappaB and prevent oxidative, hypoxic, ischemic injury to oligodendrocytes and neurons – vitamin K deficiency therefore results in classic expression of the inflammatory response and consequently pain; currently prescribed warfarin.

- 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 a proton pump inhibitor therefore advisable to check B12 status.

- 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 a proton pump inhibitor which decreases magnesium absorption.

Mrs AAQ is in the difficult position of having chronic pain whilst a proton pump inhibitor is prescribed. Advisable to 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 AAQ has been prescribed warfarin since admission and likely before then; warfarin antagonises vitamin K availability. Vitamin K is important in a range of body functions including the clotting cascade, bone health, glycaemic control, lipid metabolism, and production of myelin sheaths and neuronal membranes; and low vitamin K status is now being associated with cognitive impairment. Staff advise she eats very small serves at mealtimes, and given the duration of warfarin prescription, it is likely Mrs AAQ has a low vitamin K intake and has probably depleted her vitamin K stores. Advisable to check vitamin K intake for 3 days and clarify adequacy of intake - aiming for a minimum intake of 90 mcg/day; if inadequate intake of vitamin K and/or low blood vitamin K levels then a vitamin K tab may be an appropriate intervention to consider.

Thiamine transporters inhibited by somac and metoprolol; currently also prescribed a thiamine supplement that is presumably administered at a similar time to somac and metoprolol. If the thiamine supplement is administered first then it will reduce transporter availability for the 2 prescribed drugs ie reduce their effectiveness, and if either of the 2 drugs are administered first then thiamine absorption is significantly reduced. An interesting question is whether somac and metoprolol compete with each other for spots on the thiamine transporters.

What else would you include?

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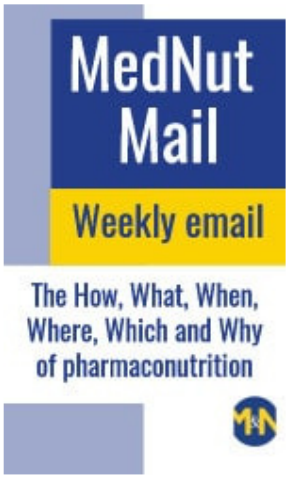

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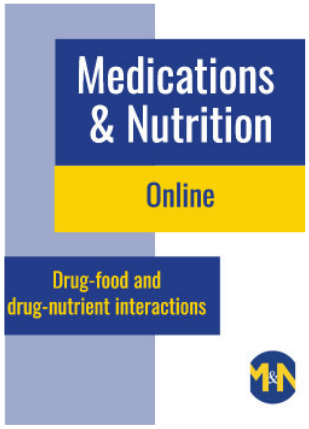

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