MedNut Mail

The How, What, Which, Where, When and Why of pharmaconutrition

Aspirin-folic acid interaction

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Editorial

An aspirin-folic acid interaction was a recent “incidental finding” from a pooled analysis of some studies looking at brain atrophy response to a B vitamin intervention. The population-based studies consistently identified a negative aspirin-folic acid interaction in those with cognitive impairment, however the mechanism(s) of action remains speculative.

The aspirin-folic acid interaction was initially discovered in the 1970’s, and subsequently referred to in many texts published in the 1980s, 1990s, and 2000s. Clinical management strategies were never developed and so the interaction was “forgotten”. The attitude/belief that “old” research is not valuable is also a likely contributor to its “forgotten” status.

Proposed mechanisms of action include -

1. **Regulation of DHFR response**. Folic acid is a synthetic form of folate that is ultimately converted to tetrahydrofolate by dihydrofolate reductase (DHFR). By inhibiting protein “E2F-1”, aspirin can regulate DHFR expression. Inhibition of DHFR upregulation can cause increased serum levels of unmetabolized folic acid. There is concern that unmetabolized folic acid may impair the transport of active folates into the brain.
2. **Inhibition of RFC-1**. The reduced folate carrier-1 (RFC-1) transports reduced folate into the brain, and its inhibition will likely result in cerebral folate deficiency. The aspirin hydrolysate salicylic acid is a likely low-affinity inhibitor of RFC-1.

The evidence across the decades consistently indicates that aspirin consumers are at risk of impaired folate status, and that folic acid interventions are ineffective.

Clinical Considerations

If a folic acid intervention is to be considered when aspirin is prescribed then when would be the best time to administer it?

Given the recommended timing for aspirin administration is with food, perhaps folic acid interventions should be administered one hour prior to the same meal, to minimise exposure to any inhibitory effect.

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Clinical Questions

What actions will you initiate as you a review a person whose prescribed medications include aspirin, will you –

- recommend regular monitoring of folate status?
- consider recommending a folic acid intervention, and at what time?
- if a folic acid intervention is prescribed and folate levels are high or at the high end of the acceptable range, will you question inhibition and therefore review administration time of the intervention in relation to aspirin administration?
- recommend the Medications Advisory Committee develop guidelines for folic acid administration when aspirin is prescribed?

Conclusions

The aspirin-folic acid interaction has been recently rediscovered. Perhaps this time clinical management strategies will be developed and introduced to ensure its long-term negative impacts do not continue.

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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: macular degeneration

Other: GORD, blindness, bilat cataracts

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
Cholecalciferol	(1000 IU/day)	☐					☐				☐	☐	☐
Citalopram	Na	☐	NV	CD	↑	↕	☑		↑		☑	☑	☑
Metformin	(08:00) B12, B1, Mg, Zn, B6, E	☐	NV	D	↓	↓	☑				☐	☐	☑
Paracetamol	Fe	☐	NV	CD			☐				☐	☐	☐
ZINCAPS	Cu	☐	NV	D			☐				☐	☐	☐
		▩					▩				▩	▩	▩

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Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OCT3		THTR2		OCTN1		MATE1		MATE2		OAT1	
Nutrients - Substrates	B1, choline, carnitine		B1, choline, NMN, carnitine		B1		B1, B6		carnitine		B1, NMN		B1, NMN		B9, B5, B6	
Nutrients - Inh																
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
Citalopram		Y		Y	Y											
Metformin	Y	Y	Y		Y		Y		Y				Y			
Paracetamol																Y
Sub – substrate, Inh – inhibitor, B1 – thiamine, B2 – riboflavin, B3 – niacin, B5 – pantothenic acid, B6 – pyridoxine, B7 – biotin, B9 – folic acid, B12 – cobalamin, NMN – N-methylnicotinamide																

Comments – medication and nutrition effects only

Data summary

Biochemistry

No recent relevant biochemistry available.

Glycaemia

BSLs (Aug-Oct) –

Before breakfast - 6.3-8.1; recommended range 4-6

Tested weekly.

Reportable limits: < 4 and > 20.

HbA1c indicates very good overall glycaemic control.

Diabetes drugs

- metformin has a duration of 12 hours

Diabetes drugs coverage

- before breakfast BSLs - no coverage from previous morning's metformin;
- before evening meal BSLs - covered by current morning's metformin.

Currently prescribed 3 medications that alter glycaemia.

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Pharmaconutrition

Currently prescribed 4 medications that include nausea, vomiting and diarrhoea as side effects.

Currently prescribed 3 medications that include anaemia glycaemia and XX as side effects.

Currently prescribed X medications that include XX and XX as side effects.

Coffee inhibits colecalciferol uptake by osteoblasts (bone builders) by inhibiting their vitamin D receptors, and consequently decreases calcium and zinc absorption therefore regular monitoring zinc status recommended.

Both citalopram and paracetamol are CYP1A2 inhibitors (blocks transporter function). CYP1A2 substrates include caffeine, retinol, melatonin, phosphatidylcholine, inhibitors include grapefruit juice and inducers include coffee; drug's metabolism inhibited therefore the drugs will remain active in the body for longer.

Regular monitoring sodium levels recommended whilst citalopram prescribed.

Metformin decreases Mg, Zn, B1, B6, folate, and B12 absorption - there is now a recommendation that B12 levels be checked on a regular basis ie at least annually; advisable to also monitor Mg, Zn, B1, B6, folate on a regular basis ie at least annually.

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

Concurrent ingestion of paracetamol and iron resulted in 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.

Longterm zinc administration may cause copper deficiency as they share the same absorption mechanism.

Zinc caps have been prescribed since 02/18, and sozole intervention has been ceased therefore advisable to check zinc levels and if > 11 units then review necessity for its continued prescription.

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

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The identified membrane transporters inhibit the absorption and/or organ and cellular uptake of thiamine, choline, carnitine, NMN (B3), pyridoxine, folate, and pantothenate which means blood test results are likely to indicate normal or elevated status whereas these nutrients may be in the blood because they are prevented from entering relevant organs and cells. Advisable for blood tests to be conducted several hours after administration of relevant prescribed medicines.

Bowel management

No regular intervention prescribed.
No PRN interventions prescribed.
No Nurse Initiated interventions administered.

Staff comments

Staff advise Mrs ACQ eats well and does not have significant food restrictions.

Observations

Mrs ACQ is a small lady with a large abdo and who was lying on her bed when I went to speak to her - she told me she eats well, sleeps well, does not feel upset in the tummy, and sometimes goes outside if the sun is shining.

Mrs ACQ has remained remarkably weight stable about 58 kg for the last 3.5 years.

Pharmaconutrition comments

Metformin is administered in the mornings therefore advisable to check afternoon/before-evening meal glycaemia for 3 days and clarify status. Staff advise Mrs ACQ does occasionally graze in the afternoons. Mrs ACQ's diabetes management includes 1 drug administered before breakfast and which has a duration of about 12 hours. If the 3 days of afternoon glycaemia monitoring indicate hyperglycaemia then it could mean -

1. current medication management strategy is undermedicating glycaemic control and therefore requires review;
2. current medication management strategy is overmedicating glycaemic control and causing the liver to release stored glucose as a hypoglycaemia management strategy and therefore medication strategy requires review;
3. current medication management strategy is overmedicating glycaemic control and Mrs ACQ is grazing to offset the hypoglycaemic effect and therefore medication strategy requires review;
4. current medication management strategy is overmedicating glycaemic control and causing both the liver to release stored glucose and Mrs ACQ to graze and therefore medication strategy requires review.

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Mrs ACQ's diagnoses include arthritis which means 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;
- 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 metformin therefore advisable to check B12 status. There is disagreement between pathology ranges and research findings with regard to appropriate B12 levels - neuro-imaging evidence indicates B12 interventions are effective once levels are less than 300 pmol/L;
- 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 metformin which decreases magnesium availability.

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

- low B12 - is important in the righting reflex when a person stumbles; prescribed metformin therefore advisable to check status;
- low magnesium - magnesium is important in vitamin D activation and muscle function, amongst other functions. Also currently prescribed metformin which significantly decreases magnesium availability. Magnesium is an intracellular ion therefore serum levels are unlikely to detect early depletion of status Advisable to clarify magnesium status.

Mrs ACQ's diagnoses include diabetes and gout – and both are now linked to dysfunctional mitochondrial. Some key nutrients in mitochondrial function include -

- magnesium citrate – important in the electron transport chain (etc) and oxidative phosphorylation;
- thiamine – deficiency impairs oxidative phosphorylation.

Both of these nutrients are negatively impacted by metformin prescription.

What else would you include?

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The information in this article is provided to support Health Professionals. It is not an exhaustive protocol and Health Professionals are advised that adequate professional supervision is accessed to ensure that Duty of Care obligations with respect to safe administration of medicines is met for each consumer.

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