MedNut Mail

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

Elevated pyridoxine and pharmaconutrition

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https://medicationsandnutrition.online

Guest case study

This email is based on a question from a reader.

I have a curious case study - 89 year old lady with peripheral neuropathy in feet that started a few months ago.

No change in medications or supplements - taking Magmin bd, Amlo, temazepan, Panadol osteo, Lyrica, Chlorsig.

Lean at 43 kg 153 cm – BMI.

Renal function eGFR - 67, other path WAL (within acceptable ranges) except for raised cholesterol - 7.0, magnesium level 0.81, thiamine 190, B6 1178, B6 10 days later 338.

B6 intake from diet 1.5 mg - spot on the RDI, other nutrients 75 - 100 % - no standouts there. She is taking 1 dspn of wheatgerm a day. Fluid intake good.

Am curious as to potential B6 hiding in supps and medications ? or as the neurologist says are we looking at the hypophosphataemia ??

Phone call discussion established there has been significant dietary change.

The short answer to the question *is B6 an excipient or hidden somewhere* – is no.

And the short answer to the question *is it hypophosphataemia* – is don't know.

The longer answer is that this Case Study highlights a currently unrecognised potential food-drug/food-nutrient interaction.

In looking for answers I came across a paper whereby the author (A) referred to research that found elevated B6 was common in adults with kidney transplants and that study team attributed the elevated B6 to dietary intake and supplements; the author(A) then investigated B6 status in paediatric kidney transplant population and found elevated B6 in 20% of his study population – this study had included dietary and supplement intake and found they were not excessive.

From these 2 papers one can ask "if the intake is not excessive then is there a problem with some aspect of the excretory system?"

Vitamin B6 is a generic name for about 6 different compounds and is important in a range of functions including -

- the metabolism of one-carbon units, carbohydrates, lipids, amino acids and proteins,

- cognitive development - via the development of neurotransmitters, and the maintenance of normal homocysteine levels,
- gluconeogenesis and glycogenolysis,
- immune function,
- haemoglobin formation.

Pyridoxine homeostasis reflects the balance between

1. dietary intake,
2. exogenous biosynthesis - from the gut microbiota,
3. renal reabsorption,
4. probably transporter influencers.

Pyridoxine absorption requires dephosphorylation for absorption and then rephosphorylation post absorption; this is probably why the neurologist was asking about hypophosphataemia. Pyridoxine absorption mainly occurs in the jejunum.

OATs (Organic Anion Transporters) transport small, amphiphilic organic anions of diverse chemical structures. OAT1 and OAT3 are strongly expressed in human kidney and localized at the basolateral membrane of the proximal tubule. OAT1 is known to play a central role in the renal uptake of a wide range of xenobiotics, including endogenous metabolic waste products, environmental toxins (which includes some toxic metals), and numerous clinically important drugs such as antibiotics, antivirals, anti-inflammatory drugs, diuretics, and anticancer agents. OAT3 transports larger and more lipophilic compounds than OAT1 and can transport drugs such as cimetidine, famotidine, and ranitidine.

Flavonoids are a class of polyphenolic compounds that are deemed extremely safe. Flavonoids are widely present in fruits, vegetables, and beverages and are the main components of a large number of herbal supplements. Flavonoids have been reported to have many beneficial pharmacological effects, including antioxidative, anti-inflammatory, and anticancer properties. A small study identified some flavanoids with significant inhibitory effect on OAT1 transporter including iochanin A, chrysin, fisetin, galangin, luteolin, morin, myricetin, and silymarin, with the following producing the greatest inhibitory effect on OAT1 -

- Fisetin is found in various fruits and vegetables, such as strawberry, apple, persimmon, grape, onion, cucumber, etc;
- Luteolin is found in celery, broccoli, green pepper, and parsley as well as the flower of Chrysanthemum morifolium, etc
- Morin is found in Osage orange, common guava leaves, and old fustic (a natural yellow dye derived from *Chlorophora tinctoria,* or *Maclura tinctoria* of the mulberry family, Moraceae.), etc
- Genistein is found in soybeans, fava beans, chickpeas, soy products, etc

- Quercetin in found in high concentrations in a few foods such as onion, asparagus, and berries, and small quantities are found in many different fruit and vegetables, etc.

As OAT1 and OAT3 have substantial overlap in substrates and inhibitors, and considering the potent inhibitory effect of flavonoids on OAT1, (the authors of the small study) anticipate that these flavonoids may also inhibit OAT3.

Other identified foodstuffs that inhibit OAT1 include -

- Epigallocatechin-3-gallate (green tea)
- methylxanthines (caffeine, theophylline, theobromine)

- *caffeine* - tea, coffee, cola, chocolate, some carbonated drinks, guarana, cola nuts;
- *theophylline* - tea;
- *theobromine* - cocoa, chocolate, tea, cola nuts.

We don't know this person's life and work history and so could ask questions relating to potential exposure to toxic metals in general such as living near/downwind of a mine or working in an industry or industrial area that includes toxic metal exposure in some way - toxic metals can be substrates and/or inhibitors of OAT1/3. Mercury is a prolific pollutant that is transported into the kidneys by OAT1/3 and is excreted into the urine by the Multidrug resistance-associated protein 2 (MRP2) ie it shares the same renal pathway as vitamin B6. Given mercury is cumulative and remains in the body for an extended period it probably has greater access to the transporters than B6 and can therefore inhibit them for extended periods. Until recently, mercury-based amalgams were a significant component for dentition maintenance ie don't forget to ask about dental fillings!

Pyridoxine is transported into the kidneys by the transporters OAT1 and OAT3; inhibition of these transporters means pyridoxine is not transported and therefore there is a build-up of pyridoxine in the blood.

Seemingly amlodipine, paracetamol, pregabalin, temazepam and theophylline are not associated with the transporters OAT1 and OAT3 – actually I am uncertain whether the research has been conducted to clarify whether there are interactions between these drugs and OAT1/3.

On the basis that there is no obvious drug involvement it seems likely the excessive B6 was due to dietary choice.

However, coadministration of OAT1/3 substrates (food, xenobiotics such as medicines, toxic metals) with potent OAT1 inhibitors may lead to increasing drug toxicity and reduced drug effectiveness – this may potentially mean a drug-food interaction and

possible food restrictions. The most well-known example of this type of interaction is drug-grapefruit juice interactions.

What interventions will you initiate when you see someone prescribed a drug that inhibits OAT1/3 – will you -

- request B6 status be clarified?
- review dietary intake for known identified OAT1/3 involvement?
- check for mercury exposure and levels?

Conclusions

Whilst this may not be a straightforward pharmaconutrition case it does highlight the pending issue with drug-food and drug-nutrient interactions in relation to transporters ie not only do we need to know which transporters carry which nutrients and which xenobiotics (prescribed medications, toxic metals) but also the foodstuffs and/or their components that are also substrates and/or inhibitors of the transporters. It is possible that in the future it will become standard clinical practice to manipulate the diet to accommodate the consequences of the xenobiotics on transporters – we are already doing this with grapefruit juice exclusion and warfarin diet.

My response to the request.

Whilst it is stated “no changes in medications or supplements” were there any dietary changes in the 6 months prior to expression of the peripheral neuropathy?

I find it curious that the magnesium levels are at the lower end of acceptable range – especially given this person is prescribed a magnesium supplement (admittedly providing only a small amount of elemental magnesium 37.4 ie mg bd) and is reported to have a high fruit and vegetable intake. There is a very small study that found high-dose vitamin B6 (100 mg twice a day for four weeks) enhanced magnesium concentrations in plasma and red blood cells – speculatively, perhaps the sustained elevated B6 levels in this person are also enhancing sustained cellular magnesium uptake and may be the reason why the magnesium levels are marginal.

It seems unlikely this case study involves pharmaconutrition – and some of that decision is based on lack of available research. It seems possible to me that one or more of the prescribed medications could be inhibitors for transporters OAT1/3 and OAT1/3 inhibition would result in excess B6 in the blood.

Advisable to exclude mercury exposure as it is a known inhibitor of OAT1/3.

Given there has been significant dietary change since original diagnoses and that the B6 levels have dropped by about 60% it seems likely the dietary intake may be the primary contributor to the elevated B6 levels.

It also seems likely to me that the potential risk of a drug-food and/or drug-nutrient interaction in this case study has just highlighted that drug-food and drug-nutrient interactions have become a lot more complicated. As the evidence increases, we may have to juggle dietary restrictions for individual drug prescriptions to minimise transporter(s) inhibition and their related consequences. For example, if a food is consumed that inhibits OAT1/3 then any drug that is transported by it will remain in the blood ie higher drug levels means increased risk of toxicity, or alternatively if a drug is prescribed that inhibits OAT1/3 then any nutrient transported by that drug will remain in the blood stream – and in the case of B6, is likely to cause toxicity problems with peripheral neuropathy.

We don't know factors such as

- the duration of OAT1/3 inhibition,
- whether the duration of inhibition is unique to each inhibiting substance,
- whether the duration is common across substances,
- the extent of food-induced OAT1/3 inhibition.,
- whether food-based OAT1/3 inhibitor intake is dose-dependent and/or cumulative.

I also suggest this case study is written up and both -

- submitted to a journal, and
- presented at a professional conference.

Practical case studies are very useful for busy clinicians!

What else would you include?

Note - it is likely this case study will have a sequel.

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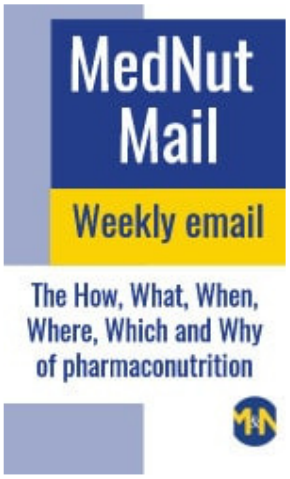

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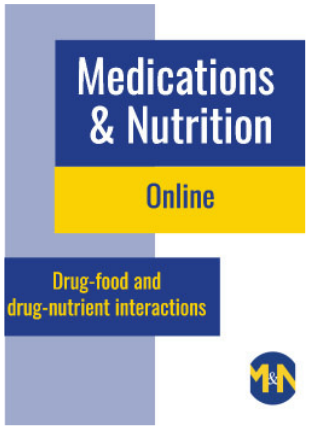

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