MedNut Mail

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

Inhibition of nutrient transporters

Y Coleman

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https://medicationsandnutrition.online

Commentary

Elevated blood levels of nutrients are currently neither looked for nor considered to contribute clinically to disease processes and so remain unrecognised and untreated.

With the advent of significant “drug” transporter research, our understanding of the extent and potential extent of prescribed medications and other substances on nutrient availability for body function is steadily growing and with that there is an increasing awareness that these issues will need to be identified and treated.

There are 4 identified mechanisms by which prescribed medications interact with nutritional factors, being alteration to –

1. food intake

- directly by altering appetite;
- indirectly through their constellation of side effects that alter taste, bowel function, mouth moistness, feeling nauseous, vomiting, etc.

2. nutrient absorption

- directly by inhibiting nutrient uptake with current identified mechanisms being drug as a substrate and occupying the transporter or drug inhibiting transporter function for an unknown period of time,
- indirectly by altering gastric pH, bacterial overgrowth, altering gut microbiome composition;

Whilst nutrient absorption is commonly associated with transfer of nutrient from gut to epithelium for further distribution, it can also apply to organ uptake of nutrients from the bloodstream.

3. nutrient metabolism

- mechanisms include altering the rate of metabolism, inhibiting nutrient availability such that metabolic processes travel alternate pathways.

4. nutrient excretion

- mechanisms include increasing or decreasing nutrient excretion and/or increasing or decreasing renal nutrient resorption;

Whilst nutrient excretion is commonly associated with renal function it can also apply to organ to blood excretion of nutrients.

Inhibition of the physiological transporters means there is a build up of nutrients in the bloodstream with nowhere to go – we know excess B6 causes peripheral neuropathy, and that excessive folic acid and B12 levels

are associated with cognitive impairment, however we don't know about the consequences of elevated levels of other nutrients nor how their excess levels are expressed.

Further, inhibition of the physiological transporters means an inadequate supply of nutrients into organs and cells ie manifesting as nutrient deficiencies. When we see normal or elevated nutrient levels in the blood we do not consider nutrient deficiency in the cells – and we are probably seeing expression of this on a regular basis and not recognising it.

At present the research seems to be focussing on the transport of nutrients from the gastrointestinal tract into the epithelium, into the liver, into the kidneys, and to a lesser extent from kidneys into the urinary system. It seems to be a very curious researcher who looks at the transporters in the cochlear's hair cells.

Questions that require answers include -

- are pathology upper limits for acceptable nutrient ranges set too high? Most pathology ranges are based on current population ranges – and the averages are therefore at risk of being higher than levels that may be physiologically safe. If the pathology upper limits are set too high then it is also likely a range of nutrients could have excess blood levels that are deemed to be within acceptable ranges - are we already seeing this and not recognising it?
- do elevated nutrients in the blood cause harm or is the harm caused by the consequent lack of availability of nutrients in the organs and cells? Or are elevated nutrient levels a symptom of harm related to the deficiency ie correlation and not causation?
- which toxic metals inhibit which transporters? are the current ranges for their presence in foodstuffs acceptable? and what is the duration of their inhibition?
- which herbicides inhibit which transporters? are the current ranges for their presence in foodstuffs acceptable? and what is the duration of their inhibition?
- what impact does the disease process have on transporter function? Examples include 50% reduction in the expression of OAT1 and OAT3 mRNA in the diabetic kidney, and in Huntington's disease there are fewer SVCT2 (sodium vitamin C transporter 2) transporters, many of which are deformed.
- is inhibition of the physiological transporters caused by the presence or absence of specific substances or is the response dose related?
- which foodstuffs, herbs and herbal supplements are

substrates and/or inhibitors of transporters?
- what is the duration of inhibition of each inhibitor on each transporter?

There is very limited research on the impact of foods, herbs and herbal supplements on physiological transporters, however it is clear that they also confer substrate and inhibitor effects. The complexity of ascertaining foodstuff, herbal and herbal supplement inhibition of transporters is exampled by cigarette smoke condensate (CSC). Evidence shows that CSC variously impacts 14 renal and non-renal transporters with the level of inhibition ranging from marginal to strong. This level of complexity may partially explain why there is such limited research into the impact of foods, herbs and herbal supplements on physiological transporters.

In relation to CSC researchers make comments such as … *the effectiveness of (identified drugs) may be compromised in smokers*, and … *inhibition due to smoking may contribute to the variable toxicity of cigarette smoke*.

What interventions will you initiate when you see someone prescribed a drug that inhibits a nutrient transporter – will you -

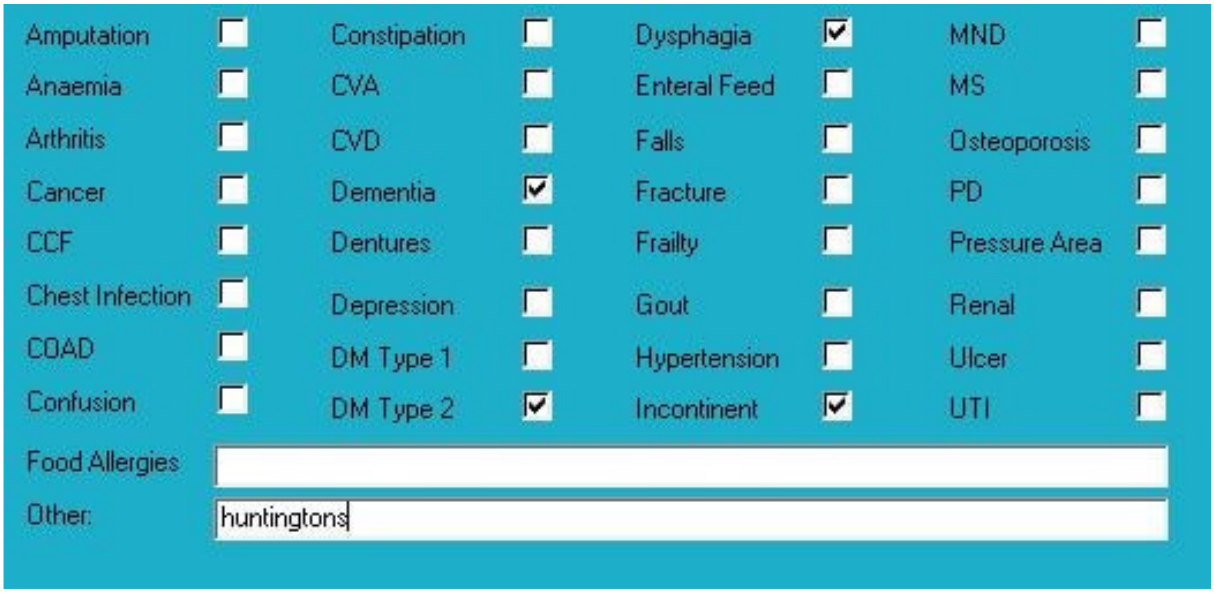
- request that nutrient's status be clarified?
- If you identify an elevated nutrient level and excluded supplements as the cause, then will you look for that vitamin's deficiency symptoms?
- pay particular attention to nutrient status and transporters if the person is a smoker?

Conclusions

It feels as though we clinicians are working in the dark, applying first principles (do no harm) and hoping answers will be available soon. It seems as though the current research is raising more questions than are being answered or appropriate management strategies developed.

Case study

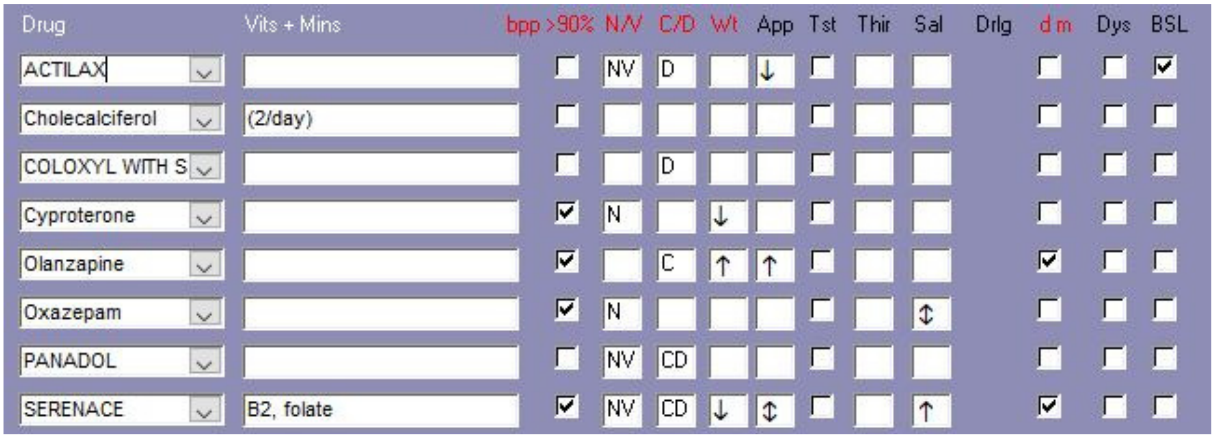
Medical History with Nutritional Aspect



Biochemistry with Pharmaconutritional Consequences

No recent relevant results available that may have a pharmaconutrition component.

Medications That May Adversely Affect Nutritional Status



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

Recent relevant available biochemistry indicates

- low Fe + low satn - short term (90-120 days) iron intervention may confer benefit

Advisable to check plasma proteins (albumin, total proteins) as markers of nutritional status. The plasma proteins are the primary transporters for 4 of the prescribed drugs and hypoproteinaemia may alter their effects and side effects.

BSLs (May-Jun)

- before breakfast - 5.1-6.2; recommended range 4-6

- daily range - 5.1-8.9; recommended range 4-10

Mr ABQ currently seemingly has well-controlled glycaemia and is not prescribed medications for its management.

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

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

Concurrent ingestion of Panadol 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.

Tegretol decreases biotin and carnitine absorption and decreases availability of folate and vitamin D.

Mild to moderate Tegretol-induced hyponatraemia may manifest as lethargy, cognitive, slowness, headache, dizziness and nausea whilst severe drug-induced hyponatraemia may manifest as falls, seizure, aggravation and hospitalization; the authors comment regular monitoring of sodium levels should be a routine component of clinical practice.

Bowels –

- regular aperients prescribed,
- oral + anal PRN interventions prescribed,
- no Nurse Initiated interventions administered.

Both staff and Mr ABQ's wife advise he eats well.

Mr ABQ is a tall, slender, pale man who was sitting in the Dining Room when I went to speak to him - he was very drowsy and had to be woken to eat each mouthful of food.

Three drugs are associated with anaemia, being cyproterone, paracetamol, Serenace.

Four drugs are associated with hypertriglyderidaemia and/or hypercholesterolaemia, being hypertriglyceridaemia, hypercholesterolaemia, being olanzapine, haloperidol, Seroquel and Tegretol.

Four drugs are associated with hyperglycaemia, being olanzapine, Panadol, Serenace, Seroquel therefore advisable to monitor Mr ABQ's glycaemic control on a regular basis.

Evidence now indicates biotin is important in glycaemic control, the TCA cycle in energy metabolism, protein synthesis and degradation. Longterm inadequate biotin intake is associated with increased risk of developing diabetes, poor glycaemic control, and weight gain. The anticonvulsant drug Tegretol competitively inhibits biotin absorption therefore advisable to consider a short term biotin intervention administered at a different time from the Tegretol.

Staff advise commented Mr ABQ frequently dozes during the day. Thiamine is important in glycaemic and lipid control, neurological function and energy production and when there is insufficient thiamine then food is converted to alternatives such as fat stores, cholesterol and triglycerides; drowsiness can be an indication of inadequate thiamine availability. Diabetes is associated with increased urinary excretion of thiamine. Currently prescribed olanzapine, haloperidol and quetiapine which all inhibit liver uptake of thiamine, and olanzapine and oxazepane are also associated with inhibition of renal uptake of thiamine, therefore Mr ABQ may benefit from a short term (90-120 days) thiamine intervention.

What else would you include?

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