MedNut Mail

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

Levodopa +carbidopa and copper

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19th June 2024

https://medicationsandnutrition.com/mednut-mail/

Editorial

Levodopa + carbidopa and copper interactions are quite complex and not always apparent. The copper-iron and copper-zinc interactions add an extra layer of complexity that is not necessarily well understood.

Parkinson's disease is attributed to loss of dopamine neurons in the substantia nigra, and loss of cells in the hypothalamus. As a cure for PD (Parkinson's disease) is not yet available, treatments focus on delaying its progression.

Astrocytes function as intermediaries between neuronal cells and capillaries to the Blood Brain Barrier and consequently may regulate brain copper metabolism.

Copper's range of functions encompasses memory and learning, responses to stress and injury, emotional well-being, circadian rhythms, and lipid metabolism. Copper deficiency is associated with iron accumulation, reduced cuproenzymes in the brain, hypochromic anaemia, neutropenia, osteoporosis, and neurological diseases. Copper excess harms include increases in oxidative stress, protein aggregation, insulin resistance, cell death, and others.

Terms

Copper in blood plasma is variously known as "free" copper, "extractable copper", "exchangeable copper", or "non-ceruloplasmin copper".

Direct interactions

Genotoxic damage is defined as substance damage to DNA that causes mutation. Genotoxic damage is only stimulated when cells are treated with levodopa or dopamine in the presence of copper. Both levodopa and dopamine can react with Cu2+ to produce Cu1+ - Cu1+ is responsible for causing DNA strand breakage. Copper concentrations in disorders such as PD, are postulated to be sufficiently increased to potentiate DNA damage. Levodopa has a higher binding affinity for DNA and consequently causes slightly higher levels of DNA breakage than dopamine.

Indirect interactions

1. Ceruloplasmin (CP)

Ceruloplasmin is a copper-dependent protein that carries more than 90% copper in plasma. CP's functions include –

- maintaining activities of copper-dependent enzymes, including SOD1 and SOD3, that are important in the removal of ROS (reactive oxygen species);
- altering iron's oxidative state to enhance its movement into and out of cells and consequent distribution by transferrin.

Decreased copper is associated with reduced ceruloplasmin and consequent increased iron accumulation in cells, including in the substantia nigra.

2. Copper-zinc superoxide dismutase 1 (SOD1)

SOD1 is responsible for removing harmful ROS molecules from cells and its activity is dependent upon copper and zinc concentrations. As an example, catalysis occurs at the copper site, and the zinc site supports the protein structure.

Cellular copper levels regulate SOD1 expression therefore reduced copper availability may contribute to SOD1 misfolding in early-disease-stage PD brain.

3. Carnosine

Carnosine is composed of the 2 amino acids alanine and histidine, and its functions include -

- specifically inhibiting hypothalamic neuronal cell death and inflammatory responses by inhibiting the ROS-JNK pathway;
- chelating zinc and copper ions.

LAT1 (large, neutral amino acid transporter 1) substrates include levodopa, histidine and the copper-histidine compound. Copper is able to stimulate histidine uptake even when LAT1 is not active.

Potentially levodopa could decrease carnosine availability by displacing histidine on LAT1. If histidine availability is reduced then endogenous carnosine levels are decreased and protection from harm is diminished. Histidine can also be recovered from carnosine and utilised to supplement dietary histidine intake in the short term. However, sustained dependency on supplementary histidine from endogenous carnosine would deplete the reserves of both.

A recent review (https://doi.org/10.3390/nu15071770) proposes carnosine as a beneficial adjunct to levodopa therapy even although the research is still minimal.

4. Hyperglycaemia

Increased copper concentration is associated with elevated ROS levels and increased insulin resistance. Insulin resistance induces hyperglycaemia which triggers further ROS, consequent further oxidative stress, and ultimately organ and cellular damage.

Several referenced papers allude to evidence of inadequate and/or excessive copper levels being associated with dysregulated glucose metabolism. The proposed mechanism of action is altered copper levels cause increased ROS production and thus physiological harm. However, it seems likely to me that copper may also directly impact glucose metabolism similarly to iron and zinc. Iron, copper and zinc are a triad of transition metals with many commonalities, and they function both independently and intradependently.

Clinical considerations

Both inadequate and excessive intakes of copper are associated directly and indirectly with negative impacts on a range of factors. The regular monitoring of copper levels and ceruloplasmin activity, at least , would be a step toward ensuring copper adequacy.

Clinical questions

What actions will you initiate as you a review a person whose prescribed medications include levodopa + carbidopa, will you -

- recommend regular monitoring of some copper status markers?
- consider the negative impacts of other prescribed medications on iron, zinc and copper levels?
- recommend regular monitoring of copper and/or a copper intervention if an iron supplement is prescribed?
- suggest trialling a carnosine intervention for a defined period and monitor for improvement?
- recommend the Medications Advisory Committee guidelines for iron supplement administration include copper intake and/or monitoring when levodopa + carbidopa is prescribed?

Conclusions

The levodopa + carbidopa and copper interactions are both extensive and not well-recognized. Maintaining adequate copper status may be quite important in slowing PD progression.

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:	® arm pain, ? Shingles						

Biochemistry with Pharmaconutrition Consequences

No recent relevant available results.

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
Aspirin	C, Fe, folate, E		☑	NV				☐				☐	☐	☑
COLOXYL WITH S			☐		D			☐				☐	☐	☐
Mirtazapine			☐	N	D	↑	↑	☐				☑	☐	☐
OSMOLAX			☐	N	D			☐				☐	☐	☐
Paracetamol	Fe		☐	NV	CD			☐				☐	☐	☐
Pregabalin			☐	NV	CD	↓	↑	☑		↑		☑	☑	☐
TARGIN			☐	NV	CD		↕	☑				☑	☑	☐

Transporter-mediated interactions and nutrients

Transporter	OCT1		OCT2		OCTN1		OAT1		OAT3		SMVT		P-gp		GLUT1	
Nutrients - Substrates	B1, choline		B1, choline		Carnitine, choline		B9, B5, pyridoxic acid (B6), B7		B5, B6, carnitine, B2		B5, B7, iodide		B12, vit D, B6, B3, B5		Vit C	
Nutrients - Inh					vit D, choline						B5, B7		vit A			
DRUG	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**	**Sub**	**Inh**
aspirin								Y	Y			Y	Y			Y
mirtazepine				Y												
paracetamol								Y								
pregabalin					Y											
Targin				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 impacts only

Data summary

Biochemistry

No recent relevant available biochemistry. Advisable to check plasma proteins (albumin, total proteins) as they are the primary transporters for one of the prescribed drugs and hypoproteinaemia may alter its effects.

Glycaemia

BSLs

- before breakfast - 3.9-5.8; recommended range 4-6;
- tested weekly;
- reportable limits: < 3 and > 25;
- advisable to check HbA1c and clarify overall glycaemic control.

Currently prescribed 5 medications that alter glycaemia.

Pharmaconutrition

Currently prescribed medications side effects include -

- 7 medications include nausea;
- 6 medications include vomiting, diarrhoea;
- 5 medications include;
- 4 medications include hypokalaemia, constipation;
- 3 medications include altered lipids, altered appetite, altered taste, dry mouth, thirst, tremor, sweating;
- 2 medications include anaemia, hyponatraemia, hyperkalaemia, altered weight, increased salivation, dysphagia;
- I medication includes – hyperuricaemia, hypernatraemia, hypothyroidism, hypoalbuminaemia, hypophosphataemia, dyskinesia.

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

Aspirin inhibits vitamin C absorption by 2 mechanisms -

1. inhibition/regulation/modulation of GLUT1 (Glucose Transporter 1) uptake of vitamin C as DHA (dehydroascorbic acid);
2. inhibition of vitamin C binding to albumin.

If there is concurrent administration of a vitamin C intervention and aspirin then advisable to administer vitamin C prior to drug as vitamin C does not impact drug absorption whereas the drug negatively impacts vitamin C absorption.

Aspirin has a negative impact on folate status - the mechanism of action remains speculative.

Caffeine increases aspirin absorption.

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

Regular monitoring sodium levels recommended whilst mirtazepine prescribed.

Mirtazepine and paracetamol are CYP1A2 substrates (can be carried by the transporter). CYP1A2 substrates include caffeine, retinol, melatonin, phosphatidylcholine, inhibitors include grapefruit juice and inducers include coffee; drug's metabolism inhibited by caffeine therefore drug will remain active in the body for longer.

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.

Some of the identified membrane transporters alter the absorption and/or organ and cellular uptake of a range of nutrients. Inhibition of membrane transporters means blood test results may be unreliable. To clarify nutrient status advisable to conduct blood tests at least one hour before administration of relevant prescribed medicines. A concurrent detailed Diet History is also essential to corroborate adequacy of intake of all affected nutrients. Further, all affected nutrients to be monitored on a regular basis ie at least annually. Unreliable blood test results due to inhibition of transporters by prescribed medications, is raising concern in some clinical publications.

Nutrients that are affected by Mr ADA's prescribed medications include -

- substrates - thiamine, riboflavin, niacin, pantothenate, pyridoxine, biotin, folate, B12, vitamin C, vitamin D, carnitine, choline and iodide;
- inhibitors – pantothenate, biotin choline, vitamin A, vitamin D.

The duration of drug inhibition of transporters currently remains unknown.

Bowels management

Regular aperients prescribed.

Oral PRN aperient prescribed.

No Nurse Initiated interventions administered.

Staff comments

Staff advise Mr ADA eats well.

Observations

Mr ADA is a well-built man who was sitting in the Day Room when I went to speak to him - he was more interested in having a drink of water than in speaking to me however he did tell me he eats well.

Mr ADA has been gaining weight during the last year.

Pharmaconutrition comments

Mr ADA's diagnoses include chronic pain. Nutritional factors that may be useful to consider in pain management 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. Currently prescribed aspirin therefore advisable to consider a vitamin C intervention. Vitamin C is not considered part of the pain management armament however it won't cause harm and evidence suggests it may confer benefit.

Nutritional factors that may be useful to include UTI management include-

- vitamin C – currently prescribed aspirin therefore intervention may confer benefit.

Curiously, Mr ADA's prescribed medications, excluding aspirin, mostly negatively impact nutritional factors by occupying or inhibiting their membrane transporters.

What else would you include?

Please read this as it is important …

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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