MedNut Mail

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

Steady state and pharmaconutrition

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24th October 2022

https://medicationsandnutrition.online

Commentary

Steady state concentration is the period during which the therapeutic levels remain constant. It is achieved when a defined amount of drug excreted is equal to the amount of drug absorbed within a defined timeframe.

The elimination half-life of the pharmaceutical determines the time to achieve steady state concentration, as outlined in the table –

Drug	Time to Steady State (SS)													
Initial dose/day	Day 1 T½	% SS	Day 2 T½	% SS	Day 3 T½	% SS	Day 4 T½	% SS	Day 5 T½	% SS	Day 6 T½	% SS	Day 7 T½	% SS
100 mg	50	50	25	75	12.5	87.5	6.25	93.75	3.125	96.875	1.5625	98.4	98.4	98.4
100 mg			50	50	25	75	12.5	87.5	6.25	93.75	3.125	96.875	1.5625	98.4
100 mg					50	50	25	75	12.5	87.5	6.25	93.75	3.125	96.875
100 mg							50	50	25	75	12.5	87.5	6.25	93.75
100 mg									50	50	25	75	12.5	87.5
100 mg											50	50	25	75
100 mg													50	50
Totals	50		75		87.5		93.75		96.87		98.4		98.4	

Steady state is achieved after approximately 5 half-lives ie about 97%.

Sometimes a defined steady state concentration is required, and within a shorter timeframe, so a loading dose is prescribed (no example shown).

Steady state concentration is essential for drug effectiveness ie whilst the blood concentrations remain within a defined range then the intervention is conferring therapeutic benefit whereas if it is -

- below the defined range then it is subtherapeutic,
- above the defined range then it is potentially toxic.

Given it is necessary for many prescribed medications to achieve steady state concentrations in order to maintain their therapeutic benefit, some questions to ponder are –

- what is the impact on physiological transporters if their substrates and inhibitors are constantly present in the blood?

- what are the short and long term nutritional consequences of steady state concentrations?
- what can we do in our clinical practice to mitigate some of the potential negative impacts of steady state concentrations on the nutritional health of those in our care?

With the realisation that steady state concentration is a significant therapeutic tool, how will you integrate this concept into your clinical practice, will you –

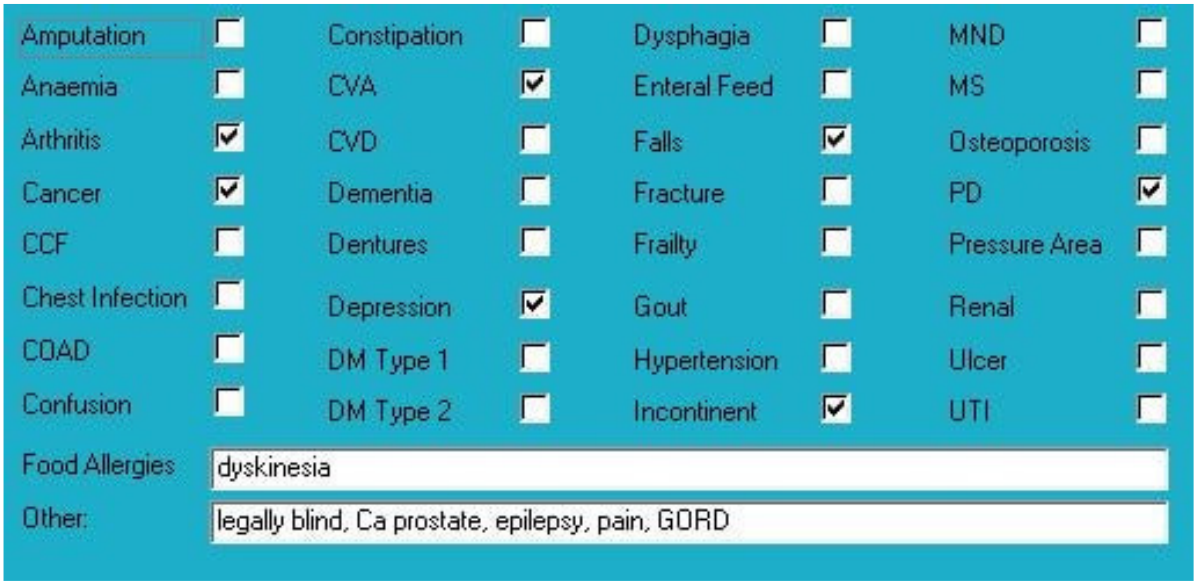
- clarify which of the prescribed medications require steady state concentrations to confer optimal therapeutic benefit?
- increase your monitoring of the nutrients known to be negatively impacted by those prescribed medications that require steady state concentrations to be therapeutically beneficial?

Conclusions

The potential negative consequences of steady state pharmaceutical concentrations on nutritional health seems to be yet another area of research awaiting perusal.

Case study

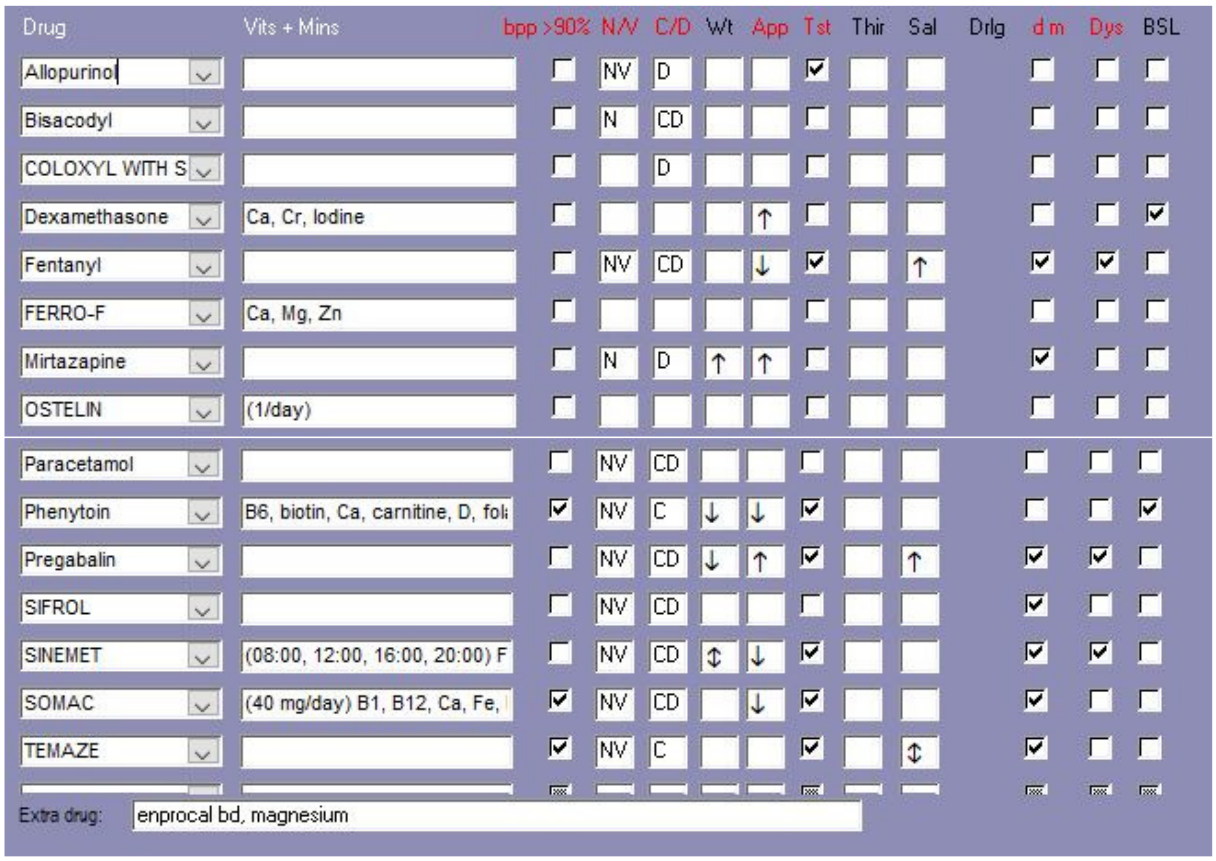
Medical History with Nutritional Aspect



Biochemistry with Pharmaconutritional 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
Allopurinol				NV	D			☑						
Bisacodyl				N	CD									
COLOXYL WITH S					D									
Dexamethasone	Ca, Cr, Iodine						↑							☑
Fentanyl				NV	CD		↓	☑		↑		☑	☑	
FERRO-F	Ca, Mg, Zn													
Mirtazapine				N	D	↑	↑					☑		
OSTELIN	(1/day)													
Paracetamol				NV	CD									
Phenytoin	B6, biotin, Ca, carnitine, D, fol	☑		NV	C	↓	↓	☑						☑
Pregabalin				NV	CD	↓	↑	☑		↑		☑	☑	
SIFROL				NV	CD							☑		
SINEMET	(08:00, 12:00, 16:00, 20:00) F			NV	CD	↕	↓	☑				☑	☑	
SOMAC	(40 mg/day) B1, B12, Ca, Fe,	☑		NV	CD		↓	☑				☑		
TEMAZE		☑		NV	C			☑		↕		☑		

Extra drug: enprocal bd, magnesium

Summary of medications and nutrients

Organ (transporter)	Thiamine	Choline	Carnitine
Inhibitor function			
Liver	Somac	Somac	
Into kidneys	Mirtazapine Sifrol Somac	Mirtazapine Somac	
From kidneys (into urinary system)			
Skeletal muscle	Somac	Somac	Somac
Substrate function			
Liver			
Into kidneys	Sifrol		
Skeletal muscle			

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

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

Glycaemia comments
Currently prescribed 5 medications that may alter glycaemia, being allopurinol, dexamethasone, phenytoin, pregabalin, Sinemet.

Bowel management comments
- regular aperient prescribed,
- oral + anal PRN interventions prescribed; oral administered 2 x Jan,
- Nurse Initiated anal interventions administered 2 x Nov.

Staff comments
Staff advise Mr ACC eats well at breakfast and that is appetite becomes very variable thereafter - some days being able to manage soft foods and thin fluids, and other days requiring smooth foods and thickened fluids.

Observations
Mr ACC is a small, pale, frail, slender man who returned from an appointment in time to talk to me. He told me he likes chocolate, strawberry and banana flavours for milk drinks, and that he prefers desserts such as chocolate mousse, crème caramel, baked rice puddings, bread and butter puddings rather than fruit and custard/ice cream.

Mr ACC has been losing weight for the last year.

Pharmaconutrition comments
Currently prescribed 11 medications that include nausea as a side effect.

Currently prescribed 9 medications that include vomiting and constipation as side effects.

Currently prescribed 7 medications that include altered taste and dry mouth as side effects.

Drugs such as allopurinol and temazepam may interact with caffeine to alter (reduce) drug effect.

Chronic use of bisacodyl may result in diarrhoea with loss of water and electrolytes, especially potassium.

Dexamethasone associated with lower vitamin D levels; vitamin D enhances the anti-inflammatory effects of glucocorticoids.

Ferro-f commenced 7 months ago - ferrous fumarate component decreases zinc absorption.

Regular monitoring sodium levels recommended whilst mirtazepine prescribed.

Currently prescribed ostelin (1/day). Advisable to check vitamin D levels and

if still low then review current vitamin D management strategy.

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

Concurrent ingestion of paracetamol and iron cause 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.

Phenytoin decreases vitamin K, pyridoxine, biotin and carnitine absorption, decreases availability of folate and vitamin D, and is associated with thiamine deficiency.

Calcium may alter phenytoin effectiveness.

Concurrent administration of pyridoxine with Sinemet reduces drug effect.

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 for at least 4 years and likely longer. There is increasing evidence that proton pump inhibitors such as pantoprazole significantly impair magnesium absorption - magnesium is important in muscle function, especially cardiac muscle, amongst other functions. 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. Currently prescribed a magnesium intervention therefore advisable to clarify effectiveness of the intervention as evidence indicates it is unlikely to confer adequate benefit.

There is increasing evidence that longterm proton pump inhibitor prescription is associated with -
- altered gut microbiome;
- increased risk of food sensitivities at the level of risk of peanut allergy;
- increased risk of coeliac disease;
- generalised malnutrition due to impaired absorption of a range of nutrients such as B12, vitamin C, magnesium, zinc, iron, etc;
- 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 review necessity for ongoing proton pump inhibitor prescription.

Mr ACC has recently had a number of falls - nutritional factors that may be contributing to his falls include -

- loss of weight - with minimal activity muscle mass is most likely being preferentially lost; weight loss likely exacerbated by three medications that include loss of weight as a side effect;
- low potassium – likely exacerbated by somac therefore advisable to check status;
- low calcium - more likely to be low if potassium or magnesium low;
- low vitamin D - currently prescribed an intervention however advisable to clarify status;
- low B12 - is important in the righting reflex when a person stumbles; currently prescribed somac which compromises B12 status therefore advisable to clarify status;
- low Hb - advisable to check status and if low, and SIS within acceptable range then may indicate sodium valproate's effect on biotin absorption - biotin is important in five stages of Hb formation;
- low iron - advisable to clarify status;
- low zinc - more likely to be low if loss of weight or prescribed a proton pump inhibitor; advisable to check status as somac prescribed, and has lost weight;
- low magnesium - currently prescribed a magnesium intervention; advisable to check status and clarify whether the intervention is being effective.

Both loss of weight and somac prescription are associated with depletion of zinc status and zinc is important in a range of body functions, including sense of taste and release of the hunger hormone Neuropeptide Y. Since Mr ACC has lost weight advisable to check zinc levels and if inadequate then short term (90-120 days) intervention and recheck status prior to cessation of the intervention; interventions are unlikely to be effective whilst a proton pump inhibitor is prescribed.

Further to discussion with staff there seem to be several main issues that result in poor appetite resulting in ongoing weight loss including total number of prescribed drugs that both directly and indirectly negatively impact appetite.

Mr ACC's diagnoses include 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 especially since phenytoin prescribed. 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;
- 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 Somac which decreases conversion of vitamin C to its active form;

- evidence indicates substantial relief of neuropathic pain by thiamine, pyridoxine and cyanocobalamin separately, and in combination there was a synergistic benefit, however currently prescribed somac (thiamine), phenytoin (B6), and Somac (B12);

- 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, and currently prescribed phenytoin.

- 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 Somac therefore 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 and damage to the brain, and recommend B12 interventions 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 Somac which decreases magnesium absorption and magnesium intervention therefore advisable to clarify magnesium status.

Mitochondrial dysfunction is now being linked to a number of disorders including heart failure, cardiovascular diseases, diabetes, neurodegenerative diseases (MS, Huntingtons, Parkinsons, MND, Alzheimers, glaucoma), ageing, mitochondrial diseases, retinis pigmentosa, CVA, epilepsy, cardiomyopathy, autism, muscular dystrophy, atypical learning disabilities, fibromyalgia, Chronic Fatigue Syndrome, Developmental Delay, Cerebral Palsy, bipolar disorder, major depression disorder, schizophrenia, pulmonary fibrosis, obesity and others. Several of Mr ACC's diagnoses fall within this umbrella therefore he may benefit

from a comprehensive nutrient intervention as we don't know the degree of increased demand being made on nutrients due to the combination of dysfunctional mitochondria and increased nutrient requirements due to negative pharmaceutical impacts.

What else would you include?

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