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

# Osmolality and prescribed medications

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# Editorial

Osmolality seems to be a rarely-considered contributor to a range of primarily gastro-intestinal side effects – and is probably overlooked because osmolality data is difficult to access; there is no regulatory requirement for its inclusion in the Product Information document.

Osmolality is a measure of the number of solute particles per kilogram of solvent and is referred to in units of mOsm/kg – further, it is also an indication of the osmotic pressure of the solution.

A formula to calculate the total osmolality of a solution (Shah et al, 2021, DOI: 10.5863/1551-6776-26.2.172) –

$$\frac{(\text{Volume}_1 \times \text{Osmolality}_1) + (\text{Volume}_2 \times \text{Osmolality}_2) + \ldots}{(\text{Volume}_1 + \text{Volume}_2 \ldots)}$$

There is a general belief that increasing osmolality causes water efflux from cells, reduction of cell volume, and crowding of the intracellular space.

**Common osmolality levels**

The currently defined acceptable osmolality limit of not exceeding 450 mOsm/kg was originally established by the American Academy of Paediatrics (AAP) in 1976 and is apparently based on a single 1975 research paper – several authors question the validity of this currently advised limit.

| Current Osmolalities of some relevant solutions | |
|---|---|
| **Solution** | **mOsm/kg** |
| amniotic fluid | 275 |
| breast milk | 300 |
| breast milk + fortifiers, nutritional supplements, medications | close to 400 |
| enteral formulas range | 240 to 365 |
| 20-kcal/oz formulas | 293 |
| 24-kcal/oz formulas | 459 |
| newborn enteral feeds | ≤ 450 mOsm/kg |

A list of 80+ prescribed medications and their osmolalities, based on papers published within the last 5 years is available as a pdf.

**Hyperosmolality consequences**

Administration of hyperosmolar oral medications alone or in combination with food or enteral nutrition may increase the risk for gastrointestinal adverse events such as -

- delayed gastric emptying,
- osmotic diarrhea,
- intestinal ischemia (restriction in oxygen availability),
- feeding intolerance,
- increased risk of necrotizing enterocolitis albeit this claim is disputed,
- increasing gastric residual volume,
- limited feeding capacity due to increased gastric residual volume,
- osmolality-dependent changes in water absorption likely causing changes in drug concentration in the gastrointestinal fluid, and potentially resulting in altered drug absorption characteristics, especially for those drugs with low permeability; this is considered to be a likely contributor to various drug-beverage interactions,
- the administration time relative to feeding time increases risk of altered clinical effect.

Strategies to reduce the osmolality to physiologically-acceptable levels include -

- diluting liquid medications with purified water in equal parts just prior to administration, however -
  - large volumes are required to achieve acceptable osmolality which are not practical in the clinical setting for neonates, especially preterm neonates,
  - the large volumes required to achieve acceptable osmolality increases risk of medication errors,
- increased administration frequency of lower-doses of prescribed medications ie same overall dose administered over a longer duration, however this strategy is associated with increased risk of medication errors.

**Inclusion in Product Information documentation?**

Several studies have identified that the osmolality of many prescribed medications significantly exceed recommended levels, and their authors consistently recommend osmolality be included in the Product Information documents.

**Clinical Considerations**

Where does osmolality impact in daily clinical practice and how can it be managed?

Fluid thickening agents for those with impaired swallow reflex –

- what is the osmolality of the various substances mixed with medicines to improve swallow safety?
- how can acceptable osmolality be achieved with each of the IDDSI defined levels of modification, especially if they seriously exceed acceptable osmolality ranges – seemingly there is potential for an undesirable trade-off between osmolality and swallow safety;

If dilution is not an option as the dilution factor may be greater than can be tolerated such as preterm babies or those who are fluid restricted, then what alternate options can be initiated to ensure acceptable osmolality?

Since apple juice has been found to increase atenolol osmolality it seems the osmolality of commonly used foodstuffs such as other fruit juices, yoghurts, apple puree, etc that are utilised in the day-to-day administration of prescribed medicines, also requires review and guidelines.

How often is enteral formula intolerance the deemed cause of intolerance when there is an alternate likely cause such as administration of hyperosmolar prescribed medicines?

**Clinical Questions**

What actions will you initiate as you a review a person with abdominal discomfort, will you –

- check the osmolality of each prescribed medicine and associated administration vehicles?
- recommend pharmaceutical review of the osmolality of their prescribed medicines if the person is not living in an institution?
- audit compliance with facility-recommended medicine administration vehicles?
- recommend the Medications Advisory Committee develop guidelines for administration of hyperosmolar medications?
- write to the TGA (Therapeutic Goods Administration), FDA (Food & Drug Administration) and EMA (European Medicines Agency) and request

osmolality of each medicine, including at each IDDSI category, be included in the Product Information documents as a standard practice?

## Conclusions

The osmolality of medications must be taken into consideration when administered alone, with enteral nutrition products, or mixed with foodstuffs as there is a likely overall increase in osmolality and its ensuing negative consequences.

## Disclaimer

*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.*

# 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: PRAWNS, ? DAIRY PRODUCTS, diverticulosis, IBS

Other: cardiomyopathy, deafness, hypercholesterolaemia

## Biochemistry with Pharmaconutrition Consequences

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Na: | 139 | mmol/l | Hb: | 125 | g/L | Albumin: | 41 | g/L | BSL: | | mmol/l |
| K: | 4.4 | mmol/l | Lymph: | 1.8 | | Total Protein: | 72 | g/L | HbA1C: | | |
| Urea: | 12.8 | mmol/l | MCV: | 106 | mmol/l | B12: | 563 | pmol/L | INR: | | |
| Creatinine: | 0.100 | mmol/l | Zn: | | umol/l | Folate: | 24.4 | nmol/L | TSH: | 0.75 | mIU/L |

Other: eGFR 42, ESR 33, CRP < 5, lactose tolerance test (07/15) normal

## 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| BICARD | | ☐ | NV | CD | ↕ | | ☐ | | | | ☐ | ☐ | ☑ |
| Candesartan | | ☑ | NV | D | | | ☑ | | | | ☐ | ☐ | ☐ |
| Cholecalciferol | (2/day) | ☐ | | | | | ☐ | | | | ☐ | ☐ | ☐ |
| Frusemide | (20 mg/day) Ca, Cl, K, Mg, Na, | ☑ | NV | CD | | ↓ | ☐ | | | | ☑ | ☐ | ☑ |
| Paracetamol | | ☐ | NV | CD | | | ☐ | | | | ☐ | ☐ | ☐ |
| PROGOUT | | ☐ | NV | D | | | ☑ | | | | ☐ | ☐ | ☐ |
| SOZOL | (40 mg/day) B1, B12, Ca, Fe, | ☑ | NV | CD | | ↓ | ☑ | | | | ☑ | ☐ | ☐ |
| SPIRACTIN | K, Mg | ☑ | NV | D | | | ☐ | | | | ☐ | ☐ | ☐ |
| SPREN | C, Fe | ☑ | NV | | | | ☐ | | | | ☐ | ☐ | ☑ |

Extra drug: probiotic cap

### Transporter-mediated interactions and nutrients

| Transporter | OCT1 | | OCT2 | | OCT3 | | OCTN2 | | SMVT | | OAT1 | | OAT2 | | OAT3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nutrients - Sub | B1, choline, carnitine | | B1, choline, B3, carnitine | | B1 | | carnitine | | B5, B7, iodide | | B9, B5, B6 | | B3, pyridoxic acid (B6) | | B5, carnitine, B6, vit C, B9 | |
| Nutrients - Inh | | | | | | | | | B5, B7 | | | | | | | |
| **DRUG** | **Sub** | **Inh** | **Sub** | **Inh** | **Sub** | **Inh** | **Sub** | **Inh** | **Sub** | **Inh** | **Sub** | **Inh** | **Sub** | **Inh** | **Sub** | **Inh** |
| Bicard | | | | Y | | | | | | | | | | | | |
| Candesartan | | | | | | | | | | | | Y | | | | Y |
| Furosemide | | | | | | | | | | | Y | | | | | |
| Paracetamol | | | | | | | | | | | Y | | | | | |
| Progout | | | | | | | | | | | | | | Y | | |
| Sozole | | Y | | Y | | Y | | | | | | Y | | | | |
| Spiractin | | Y | | Y | | | Y | | | | | | | | | |
| Spren | | | | | | | | | | 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 (B3)

BCRP substrate nutrients include B2, B9, B5, vit K3, and inhibitors include vit D2; drug substrates – Progout, Sozole

# Comments – medication and nutrition effects only

## Data summary

### Biochemistry with Nutritional Aspect

Recent relevant available biochemistry indicates –

- elevated normal TSH - evidence indicates increased risk of altered thyroid function in the elderly once TSH > 2.5;
- confirmation of lactose tolerance.

### Glycaemia

Currently prescribed 3 medications that alter glycaemia.

**Pharmaconutrition**

Currently prescribed -

- 8 medications that include nausea and vomiting as side effects.
- 7 medications that include diarrhoea as a side effect.
- 4 medications that include constipation as a side effect.
- 3 medications that include altered taste as a side effect.

Bicard may mask signs of hyperthyroidism.

Candesartan may cause altered sense of taste unrelated to zinc status.

Frusemide increases urinary excretion of calcium, magnesium, potassium and sodium.

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.

Sozole decreases B12, vitamin C, magnesium, zinc and iron absorption, may decrease calcium absorption, and decreases thiamine availability.

Spiractin plus aspirin decreases sodium excretion.

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

Currently prescribed vitamin D (2 tabs/day). Advisable to check vitamin D levels and if still low then review current vitamin D management strategy.

Currently prescribed 2 drugs that decrease riboflavin availability – being Bicard and candesartan. Riboflavin is the rate-limiter for one-carbon meatabolism and therefore altered riboflavin status significantly impacts metabolic processes.

Mrs ACO is prescribed three drugs that alter thiamine availability - being frusemide, Sozole and Spiractin. Thiamine is important in glycaemic and lipid control, and energy production; when there is insufficient thiamine then food is converted to alternatives such as fat stores, cholesterol and triglycerides. Mrs ACO is at risk of decreased thiamine availability therefore advisable to monitor status on a regular basis.

Currently prescribed two drugs that decrease magnesium availability - being frusemide and Sozole. 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 remains unknown whilst magnesium levels within acceptable range however if magnesium levels are low then that typically indicates significant cellular depletion and intervention recommended. Advisable to monitor magnesium status on a regular basis ie at least twice a year.

Currently prescribed 4 drugs that negatively impact zinc status – being candesartan, Spiractin, frusemide, Sozole. Zinc is important in multiple body functions, including glycaemic control, and sense of taste, therefore advisable to monitor zinc status on a regular basis ie at least annually.

**Bowel management**

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

**Staff comments**

Staff advise Mrs ACO eats well.

**Observations**

Mrs ACO is a small, charming lady who was participating in an activity when I went to speak to her - she told me she does not eat well but does eat enough for an old person and that old people don't need a lot of food; we had a lively discussion about her last statement.

Mrs ACO has remained weight stable about 58-60 kg for almost a year.

## Pharmaconutrition comments

Mrs ACO preferentially excludes dairy products as she believes they cause her loose bowels, therefore advisable to consider a calcium intervention. Calcium carbonate requires gastric acidity for absorption however Sozole prescribed therefore advisable to consider calcium citrate which does not require gastric acidity for absorption.

Mrs ACO has been prescribed a proton pump inhibitor for at least 6 years. There is increasing evidence that longterm (3+ years) proton pump inhibitor prescription is associated with -

- altered gut microbiome;
- increased risk of food sensitivities at a level of peanut allergy, due to partial protein digestion;
- increased risk of coeliac disease due to partial protein digestion;
- increased risk of scurvy;
- 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 reconsider reviewing current proton pump inhibitor prescription and consider -

- whether proton pump inhibitor prescription is still required,
- if suppression of gastric acidity is still required then could it be managed with an H2 antagonist such as ranitidine (there is a general belief that they cause less nutritional harm than proton pump inhibitors).

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

- B12 and/or folate - associated with deafness; currently prescribed Sozole therefore advisable to check B12 status and if low then intervention recommended;
- vitamin C - inadequate dietary intake associated with deafness; currently prescribed Sozole which reduces conversion of vitamin C to its active form;
- vitamin D - associated with low-frequency and speech-frequency hearing loss; currently prescribed an intervention therefore advisable to clarify status;
- zinc - inadequate zinc status has been associated with impaired hearing; currently prescribed Sozole therefore advisable to check zinc status and if low then intervention recommended;
- Thiamine – associated with bilateral hearing loss and proposed mechanism of action is that thiamine transporter OCT2 is expressed in the hair cells of the cochlea therefore interruptions to thiamine accessibility are likely to impact hair cell function; currently prescribed Sozole and frusemide which decrease thiamine availability both directly and indirectly.

Mrs ACO'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. 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 Sozole which decreases conversion of vitamin C to its active form.

- 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 Sozole therefore advisable to check B12 status.

- 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 Sozole which decreases magnesium absorption.

Mrs ACO'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 Sozole therefore advisable to check status;

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

- low B12 –currently prescribed Sozole therefore advisable to check B12 status.

The identified membrane transporters inhibit the absorption and/or organ and cellular uptake of B1, B2, B3, B5, B6, B7, B9, vit C, vit K3, iodide, choline, carnitine, 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.

What else would you include?

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