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Review

Effects of widely used drugs on micronutrients: A story rarely told

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ABSTRACT

Vitamins and trace elements are essential to the body, however, deficiencies are frequently observed in the general population. Diet is mostly responsible for these deficiencies but drugs also may play a significant role by influencing their metabolism. These effects are rarely assessed in clinical practice, in part because of limited data available in the literature. Drug-induced micronutrient depletions, however, may be the origin of otherwise unexplained symptoms that might sometimes influence medication compliance.

We present various examples of widely prescribed drugs that can precipitate micronutrient deficiencies. This review aims at sensitizing physicians on drug–micronutrient interactions. High-risk population groups also are presented and supplementation protocols are suggested.

Introduction

Vitamins and trace elements are essential to the organism. Required allowances are covered almost exclusively by food intake and their deficiency leads to structural or functional dysfunctions that are potentially reversible after supplementation. Despite their importance, the role of vitamins and trace elements is underestimated and studies in industrialized countries show that the prevalence of micronutrient deficiencies may exceed 30% [1]. Suboptimal nutritional intake is mostly responsible, yet several drugs and drug combinations also may be held accountable, especially in frail, older patients. Indeed, 40% of institutionalized patients take more than nine drugs on a daily basis [2]. In this population, the prevalence of zinc and selenium deficiencies may reach 50% [3].

Drugs influence the metabolism of vitamins and trace elements in many ways, from their intestinal absorption, to their bioavailability and elimination (Table 1). Drug–micronutrient interactions rarely are explored in clinical practice.

We present various examples of widely prescribed drugs that can precipitate micronutrient deficiencies. These examples were chosen in light of their clinical significance. Thus, the frequency of drug prescription, the existence of recent data in the literature, potential repercussions of the interaction on drug compliance [4,5], and the importance of the micronutrient deficiency were taken into account. Finally, the drugs chosen are frequently combined, possibly exposing patients to synergic effects on micronutrient metabolism. The analysis of the literature included all publications of the Medline database since 1970 using free, "MESH" and "MESH major topics" terms for all the drugs and micronutrients included in this article. This review aims at sensitizing physicians on drug–micronutrient interactions. High-risk population groups also are presented and supplementation protocols are proposed.

Renin–angiotensin–aldosterone axis inhibitors and zinc deficiency

Angiotensin-conversion enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARA II) inhibit the renine–angiotensin–aldosterone axis and are essential in the treatment of arterial hypertension and chronic heart failure. Pharmacovigilance reports yield evidence of taste disorders associated with these drugs [6–8], in particular the tastes of "bitterness" and "sourness" [6]. Intracellular zinc depletion has been suggested as the main underlying cause [7,8]. Indeed, various studies have associated ACEIs and ARA II to a significant decrease in serum zinc, and increases in zincuria, intraerythrocytic, and intramonocytic zinc

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Table 1
Effects of widely used drugs on micronutrients and eventual supplementation schemes

Drug or clinical condition	Concerned micronutrient	Type of effect	Risk factors/ populations at risk	RDA adults	Proposed substitution scheme
ACEI/ARA II	Zinc	↓ Cell availability ↑ Renal elimination	Age, diabetes heart failure, thiazides, institutionalization	♂ 11 mg/d ♀ 8 mg/d	25 mg/d for 6 mo [14]
Acetylsalicylic acid	Vitamin C	↓ Absorption ↓ Cell availability		♂ 90 mg/d ♀ 75 mg/d	500 mg/d [43]
PPI	Vitamin B_{12}	↓ Absorption	Age >60 y, HP infection atrophic gastritis, any cause hypochlorydria, CYP 2C19 inhibition	♂,♀ 2.4 μg/d	1 mg of IM weekly injection or 2 mg/d orally until serum levels >200 pmol/L [44]
	Vitamin C	↓ Absorption	HP infection, atrophic gastritis, any cause hypochlorydria	♂ 90 mg/d ♀ 75 mg/d	500 mg/d [43]
	Iron	↓ Absorption	Vegetarians, vegans, elders masticatory problems, iron deficiency, any cause hypochlorydria	♂,♀ 10 mg/d	According to the formula: weight [kg] × (target Hb-measured Hb) [g/L] × 0.24+ 500 mg
Metformin	Vitamin B_{12}	↓ Absorption	Vegetarians, vegans, dose >1 g/d, treatment >3 y	♂,♀ 2.4 μg/d	1 mg of IM weekly injection or 2 mg/d orally until serum levels >200 pmol/L [44]
	Folic acid			♂,♀ 0.4 μg/d	1–5 mg/d until normal serum levels
SAM	CoQ10	↓ Cell availability ↓ Endogenous production	Age >70 y, especially rigorous sport activity	♂,♀ 30 mg/d	100–200 mg/d [67]
	Vitamin D			♂,♀ <70 : 600 UI/d ♂,♀ >70 : 800 UI/d	1500–2000 UI/d [73]

ACEI/ARA II, angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists; CoQ10, coenzyme Q10; CYP, cytochrome P450; Hb, hemoglobin; HP, *Helicobacter pylori*; IM, intramuscular; PPI, proton pump inhibitor; RDA, recommended dietary allowances; SAM, statin-associated myopathy

depletions [9,10]. The underlying mechanisms of these observations remain unclear. Current data support a class effect related to the inhibition of either angiotensin II production (ACEIs) or final action (ARA II), leading to increased zincuria because angiotensin II indirectly induces zinc tubular reabsorption [10]. Captopril in particular has a thiol-radical (-SH) that can chelate with serum zinc and further increase its urinary excretion [9]. Enhanced zincuria and its consequent decrease of plasmatic zinc could potentially initiate a shift of intracellular zinc out of the cells and induce zinc depletion [11].

The interaction of these drugs with zinc is further complicated by the fact that ACEI and ARA II are usually prescribed for clinical conditions well known to disturb zinc's metabolism such as diabetes and chronic heart failure [12]. Additionally, their frequent combination with thiazides enhances their zincuric effect because the thiazides block zinc's reabsorption in the distal tubule [10].

Clinical manifestations of zinc depletion are atypical and warrant high clinical sensitivity: hypogonadism, anorexia, dysgeusia, hypothyroidism, neurosensitive disturbances, retarded healing, and vulnerability to infections. A causal relationship may be difficult to establish because some of these manifestations can be attributed to the underlying disease (e.g., diabetes). In high-risk situations for zinc depletion (Table 1), physicians should search for the symptoms described previously rather than dose serum zinc because it modestly reflects zinc's intracellular levels [13]. A positive history of these symptoms and particularly of dysgeusia or anorexia should motivate a supplementation test (e.g., with zinc 25 mg/d for 6 mo) [14], combined with a diet enhanced in copper (organ meats, meat, seafood, cereals, nuts, legumes), as zinc and copper antagonize for their intestinal absorption.

Acetylsalicylic acid and vitamin C

Previously, acetylsalicylic acid (ASA) was used in high doses for its anti-inflammatory and antirheumatic properties. Such doses had deleterious effects on vitamin C metabolism [15]. The underlying mechanisms are not fully known. Vitamin C is subject to an enterogastric circulation where gastric mucosa acts as depot with concentrations 25 times higher than in plasma [16]. Vitamin C is then secreted in the gastric juice and absorbed in the jejunum.

In a study on young healthy women, 900 mg of ASA were randomly combined with 500 mg of vitamin C in single oral doses. The ASA plus vitamin C group showed an increase of the vitamin's plasma and urine concentration, but less than the vitamin C–only group. Also, leucocyte vitamin C concentration remained almost unchanged in the first group [17]. Another cross-over study showed a 10% decrease of the vitamin C gastric mucosa content, plasma, and urine concentration after only 7 d of treatment with 2400 mg of ASA. Finally, a daily regimen of 2400 mg of ASA blunted the effect of vitamin C supplementation on the vitamin's gastric mucosa concentrations [16].

Two mechanisms have been suggested for the interaction between ASA and vitamin C: an absorption defect as denoted by the increase of vitamin C fecal concentrations in the presence of ASA [17], or a blockage of vitamin C uptake by leucocytes [18]. Overall, this interaction remains clinically insignificant, especially because ASA is currently administered in far lower doses (e.g., for cardiovascular prevention). Systematic supplementation of this vitamin in patients on ASA therefore is not recommended.

Proton pump inhibitors induce multiple micronutrient deficiencies

Proton pump inhibitors (PPIs) are among the most frequently used drugs, with especially high inappropriate prescription rates, exceeding 50% in elderly patients [19]. PPIs increase intragastric pH, thus influencing the absorption of vitamin B_{12}, vitamin C, and iron.

PPIs and vitamin B_{12} deficiency

Acid gastric milieu and pepsin are necessary to the vitamin's liberation from the dietary proteins to which it is bound, rendering it available to form its gastric complex with the R protein. The