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Interactions between drugs and micronutrients

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Drug-induced micronutrient deficiencies – homocysteine – pharmacodynamic and pharmacokinetic interactions – Phenprocoumon and vitamin K – diuretics and magnesium – statins and coenzyme Q10 – anti-epileptics and vitamin D – proton pump inhibitors and vitamin B12 – cisplatin and L-Carnitine

Abstract. Interactions between drugs and micronutrients have received only little or no attention in the medical and pharmaceutical world in the past. Since more and more pharmaceutics are used for the treatment of patients, this topic is increasingly relevant. As such interactions – depending on the duration of treatment and the status of micronutrients – impact the health of the patient and the action of the drugs, physicians and pharmacists should pay more attention to such interactions in the future. In this context, the pharmacist, as a drug expert, assumes a particular role. Like no other professional in the health care sector, he is particularly predestined and called up to respond to this task. The following article intends to point out the relevance of mutual interactions between micronutrients and drugs, without claiming to be exhaustive.

Introduction

Thanks to modern health care and the improvement of life quality, the average life expectancy of Europeans has almost doubled over the past 100 years. It is estimated that by 2010 more than 20% of the European population will be over 70 years of age. The increase in the mean age goes along with an increasing number of multimorbid patients, who suffer from nutrition-associated diseases and usually depend on complex pharmacotherapy.

Multimorbidity inevitably leads to polypharmacotherapy. Surveys on the prescription habits in German clinics reveal that a patient is given, on average, 3 – 6 different drugs during clinical treatment. Each additional medication, however, increases the risk of side effects or interactions. The problem of adverse effects has been confirmed by the results of a meta-analysis carried out by the Journal of the American Medical Association in 1998, which investigated the incidence of side-effects in clinical patients in the US. The analysis of 39 prospective studies showed that severe side-effects had occurred in 6.7% of patients, with a death rate of 0.32%. The authors estimated that in 1994 severe side effects occurred in 2,216,000 clinical patients whereas 106,000 patients died from such effects. Although the results of this analysis should not be overrated given the heterogeneity of the conducted studies, it becomes clear that adverse medical effects are of high clinical relevance and can take on critical dimensions.

Interactions between drugs and micronutrients

Micronutrients and drugs use the same transport and metabolism pathways in the body for their absorption, metabolism, and elimination. This means that when one or more drugs are taken, there is always a potential risk of interactions with the nutrient balance. As a consequence of this, the action of a drug may be adversely affected by a micronutrient (e. g. decrease in the efficacy of tetracyclines due to calcium) and similarly the physiological function of a vitamin or mineral may be impaired by a drug (e.g. antagonism of folic acid by MTX). Disruption of micronutrient levels can result in serious metabolic disturbances, as there is hardly a single physiological process in the body that is not mediated by one or another of these biocatalysts. Given the ever-increasing number of pharmaceutical products on the market and the frequency with which they are used, greater attention must now be focused in particular on the adverse effects of drug therapy on the micronutrient balance (Figure 1) in order to minimize the potential risk to the health of patients.

Vitamins, minerals and trace elements have a considerable preventive medical and

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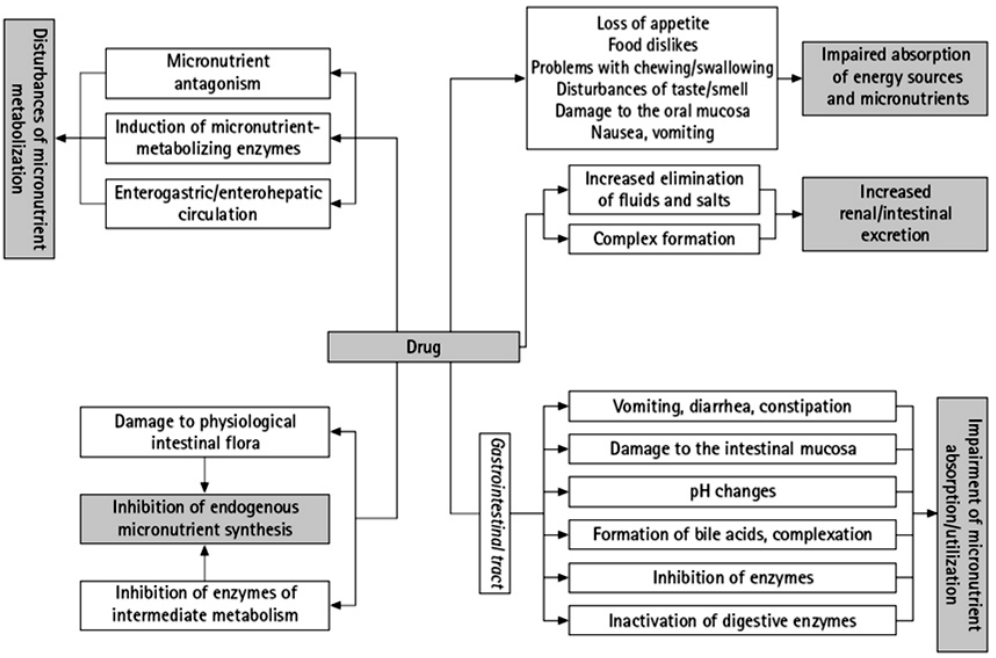

Figure 1. Disruption of micronutrient status by drugs [2].

Table 1. Drugs that may increase the level of homocysteine (Hcy).

Drug	Mechanism
a) Drugs frequently used for cardiovascular diseases	
Cholestyramine	Impairment of folic acid and cobalamin absorption
Fibrates (e.g. Fenofibrat) reduced	PPAR activation, interference with renal function, homocysteine excretion (alternatively: Gemfibrozil)
Diuretics (e.g. thiazide)	renal excretion of folic acid, B12 and B6
HCT/Triamteren	renal excretion of folic acid/folic acid antagonism
Metformin	binding of calcium, vitamin B12 absorption , folic acid/ B12-plasma level
Nicotinic acid	vitamin B6 antagonist, inhibits pyridoxal kinase
b) Further drugs	
Anti-epileptic drugs (e.g. carbamazepine, phenytoin, valproic acid)	folic acid antagonism, enzyme induction, inhibit folat absorption
Cyclosporin A	renal function , renal excretion of homocysteine
Levodopa	substrate of SAM-dependent methylation
Isoniazid	vitamin-B6 antagonist through complex formation
Oral contraceptives	interference with folic acid
Laxatives	folic acid absorption
L-Methionine	homocysteine precursor
Methotrexate (MTX)	folic acid antagonism, inhibits dihydrofolate reductase
Omeprazole	Impairment of vitamin B12 absorption
Sulfasalazine	folic acid absorption
Theophylline	vitamin-B6 antagonist, inhibits pyridoxal kinase
Trimethoprim	inhibition of dihydrofolate reductase

therapeutic potential in the prevention and therapy of nutrition-associated diseases. A disturbance of the micronutrient status can result in severe disorders of the metabolism, because almost every physiological process in the body involves one of these bio catalysts. In view of the frequency and steadily increasing number of drugs, the adverse effects of pharmacotherapy on micronutrients should be given far more consideration than in the past in order to minimize the potential risks for patients.

A number of drugs, for example, interfere with the physiological excretion of homo-

Table 2. Symptoms of marginal micronutrient deficiencies (selection) [3].

Micronutrient	Symptoms
vitamin B1	learning and concentration disorders
niacin	depression, fatigue, nervousness
vitamin B6	headache, fatigue, nervousness
vitamin B12	apathy, mental deficits, dementia
folic acid	apathy, mental deficits, dementia
vitamin C	reduced physical performance, episodes of depression, liability to infections
magnesium	tension headache, liability to stress, nervousness
iron	pallor, fatigue, liability to infections
zinc	liability to infections, poor wound healing

cysteine, an angiotoxic and neurotoxic amino acid,

- acting as direct or indirect antagonists of cofactors and enzymes
- by interfering with the absorption or biotransformation of vitamins
- and/or enzyme modulation (e.g. cytochrom-P450 enzyme induction)

which leads to hyperhomocystinemia. What this should make us think about is the fact that the list contains a number of drugs (Table 1) which are regularly used to treat cardiovascular diseases (e.g. dyslipoproteinemia, hypertonia, diabetes mellitus) without the awareness that an increase of the homocysteine plasma level (> 9 mol/l) poses a high risk to health.

Next to the necessary medication, monitoring the homocysteine levels and the supplement of 5-Methyl-THF, vitamin B_{12}, B_2 and B_6, constitute further important elements in the pharmacotherapy of cardiovascular disease to decrease the individual cardiovascular and neuro-cognitive risk!

Consequences of latent micronutrient deficiencies

In the clinical context, it has to be assumed that the dark figure of drug-induced imbalances of micronutrients is quite high, although they only seldom appear as manifest deficiency symptoms (Table 2). They rather occur as unspecific disturbances due to latent micronutrient deficiency, which expresses through lack of appetite, general weakness, learning and concentration disturbances, headaches, nervousness and increased liability to infections or stress. In the medical and pharmaceutical practice, such symptoms are often disregarded, or accepted as metabolic imbalances due to age, environment or genetics, although they considerably impact the health and well-being of the patients.

Latent deficiencies can rapidly give way to clinically manifest deficiencies, when the organism is exposed to major strains (e.g. influenzal infection, physical or emotional stress, medication). Current surveys on consumption habits and nutrition reports diagnose latent nutrient deficiencies in almost all groups of people. School children, working women and men, athletes, pregnant women and elderly people are particularly affected. If we take into account that the activity of magnesium-dependent enzymes falls by 50% when the supply of magnesium to the cells decreases by 25%, we can hardly imagine the impact of long-lasting and latent micronutrient deficiencies on our health.

Physicians of Harvard University recently evaluated scientific studies stretching over a period from 1966 to 2002 and came to the conclusion that a latently existing undersupply of vitamins considerably increases the risk of chronic diseases. Reduced absorption of folic acid, vitamin B6 and B12 represents a risk factor for cardiovascular diseases, neural tube defects as well as breast and colon cancer. Suboptimal supply with vitamin D and K increases the risk of osteoporosis. The risk of contracting radicals-associated diseases such as arteriosclerosis, macula degeneration or cancer is increased by an inadequate supply of anti-oxidative vitamins (e.g. vitamin A, E, C, lutein). As most people do not have the optimum quantity of all micronutrients, the Harvard physicians recommend that adults should daily take a food supplement containing multivitamins and mineral nutrients to prevent potential undersupply. Here they particularly stress the importance of folic acid, vitamin B6, B12 and vitamin D!

Factors influencing drug-micronutrient interactions

The use of medicinal products that affect the metabolism of vitamins and minerals does not automatically mean there is a risk of

Table 3. Drug-micronutrient interactions and influencing factors [2].

Drug
- indication, dosage and duration of medication
- absorption, distribution, biotransformation and elimination (pharmacokinetics)
- pharmacological/toxicological action profile, site of action, mechanism of action and strength (pharmacodynamics)
- physical and chemical properties (application, pharmaceutical form, galenics)
- mono- or combination therapy
- substance-substance interactions

Micronutrient
- biochemical and physiological functions
- absorption, distribution, biotransformation, storage and excretion
- physicochemical properties (e.g. fat soluble, water soluble, structure)

Patient
- age, sex, illness
- micronutrient status
- medication (including uncontrolled self-medication, supplements of vitamin preparations)
- dietary habits
- gastrointestinal integrity
- function of the liver and kidneys
- consumption of unhealthy foods/substances (alcohol, smoking, sweets)

Table 4. Micronutrient antagonists (selection).

Micronutrient	Antagonist	Enzyme (site of action)
Folic acid	Methotrexat, Tetroxoprim, Trimethoprim, Triamteren, Pyrimethamin	Dihydrofolat-reductase
Coenzyme Q10	Statins (e.g. lovastatin)	HMG-CoA-Reductase
Vitamin K	Phenprocoumon, Warfarin	Vitamin-K epoxide-reductase
Calcium	Magnesium	myocardial cell (competition for membrane calcium channels and bindings to Troponin)
Potassium	cardiac glycosides	Mg-dependent Na+/K+-ATPase

drug-induced micronutrient deficits. Of critical importance here is the duration of treatment and the nutritional status prior to the start of treatment.

As a general rule, the micronutrient status of a healthy person with a balanced diet is not adversely affected by use of pharmaceuticals for short periods. If intake of a micronutrient is already inadequate, or if a drug has been taken for a lengthy period or alongside other drugs, then interactions between micronutrients and drugs become relevant and must consequently be taken increasingly into account in diagnostic and therapeutic considerations. Those at particular risk are the chronically ill (long-term medication), the elderly (multimorbidity, multiple drug therapy), and patients who are self-medicating without seeking the advice of a doctor or pharmacist. The nature and intensity of the interaction between a drug and a micronutrient depend on a host of influencing factors (Table 3). Chief among them are the pharmacological and toxicological action profile of the drug, the duration of medication, and the patient's dietary habits and micronutrient status at the start of drug therapy.

Interaction mechanisms

Interactions manifest when the effect and/or side-effect of a substance is qualitatively or quantitatively altered by a second substance which either impacts absorption, metabolism or elimination, or causes a synergistic or antagonistic effect in a different location. Based on the underlying mechanisms, interactions between remedies and nutrients can be categorized into
- pharmacodynamic and
- pharmacokinetic

interactions in analogy to the interaction of remedies.

Pharmacodynamic interactions

Pharmacodynamic interactions between drugs and micronutrients may occur when the interacting substances have either an antagonistic or a synergistic effect on a particular site of action (e.g. enzyme) or in a closed loop. Since many micronutrients act as co-enzymes (e.g. folic acid) or co-factors (e.g. magnesium), interactions manifest especially on the enzymatic level.

The inhibition of micronutrient-specific effects on a physiological site of action (Table 4) is the therapeutic principle of specific drugs, including anticoagulants of the dicoumarol-type, antibacterial folic-acid antagonists or cardiac glycosides.

Vitamin K and dicoumarol derivates

There is a great analogy in structure between the *vitamin-K antagonist phenpro-*

coumon and the natural vitamin K. It inhibits vitamin K epoxide reductase in the so-called vitamin K cycle, thereby suppressing the carboxylation of vitamin-K-dependent clotting factors and reducing blood coagulation.

Vitamin K is not only essential for coagulation, but also for the -carboxylation of osteocalcin, a bone protein which mainly occurs in the fast growing sections of the bones. Osteocalcin (Oc) is a non-collagen glycoprotein that is produced in the osteoblasts and stimulates the formation of bones. When, because of a lack of vitamin K or during a therapy with vitamin K-antagonists, -carboxylation is blocked, the fraction of non-carboxylated osteocalcin (ucOc) in the plasma increases. Under-carboxylated osteocalcin is an important indicator for impairments in the bone metabolism. Thus it cannot be ruled out that patients undergoing a long-term therapy with anticoagulants of the dicoumarol-type are not put to a higher risk for osteoporosis. However, as large quantities of vitamin K (e.g. vitamin K preparations, vegetables) may diminish the effectiveness of vitamin K antagonists, the dosage of vitamin K should be determined depending on the Cumarine-anticoagulants-therapy, and the coagulation parameters should be closely controlled [4].

Potassium and cardiac glycosides

Depending on the concentration, cardiac glycosides bind magnesium-dependent Na+/K+-ATPase of myocardial cells and reduce the action of enzymes. This, in turn, leads to a reduced leakage of sodium ions out of the cell and influx of potassium ions into the cell. Increased intracellular sodium concentration leads to an increased calcium influx into the cell via plasma membrane Na+/Ca2+-exchanger, resulting in increased myocardial contraction (positive inotropic effect).

One disadvantage of cardiac glycosides is their narrow therapeutic bandwidth, which becomes particularly manifest in potassium imbalances. Potassium depletion (e.g. caused by thiazides or loop diuretics, laxatives) increases the effects of cardiac glycosides and thus the risk for cardiac dysrhythmia. Parenteral applied calcium salts increase toxicity as well. For this reason, injections of calcium-containing solutions are best avoided under glycoside therapy, whereas potassium (e.g., mineral nutrient preparations) or potassium-sparing diuretics (e.g. spironolacton, triamteren) reduce the therapeutic effect of cardiac glycosides.

The glycoside tolerance, however, can be enhanced with magnesium, because it regulates the potassium balance and, in terms of calcium antagonist, protects the myocardial cells from over-loading with calcium ions. It is therefore recommended to closely monitor the level of potassium and magnesium under cardiac glycoside therapy and, if necessary, use substitutes to regulate the system [5].

Folic acid and folic-acid antagonists

The antibacterial folic-acid antagonists Trimethoprim and Tetroxoprim, which are often used in combination with sulfonamide (sulfamethoxazol, sulfadiazin), inhibit the dihydrofolate-reductase in bacteria. Although the affinity to humane dihydrofolate-reductase is several decimal levels higher for the bacterial enzyme, patients treated with this drug showed impaired hematopoesis (megaloblastic anemia) and homocysteine metabolism. The same interactions can occur under therapy with the potassium-sparing diuretic Triamteren or with the Antiprotozoal drug Pyrimethamine.

Statins and coenzyme Q10

Statin drugs produce a proportional decrease of ubiquinol-10 and ubiquinone-10 levels as well as serum cholesterol levels. Some of the adverse reactions of statins (e.g. myopathic symptoms) could be a direct or indirect result of coenzyme Q10 deficiency consequent to statin treatment [6].

Pharmacokinetic interactions

Pharmacokinetic interactions between drugs and micronutrients manifest, among other things, as absorption, biotransformation or excretion processes. They usually lead to a reduced bioavailability of a drug or micro-

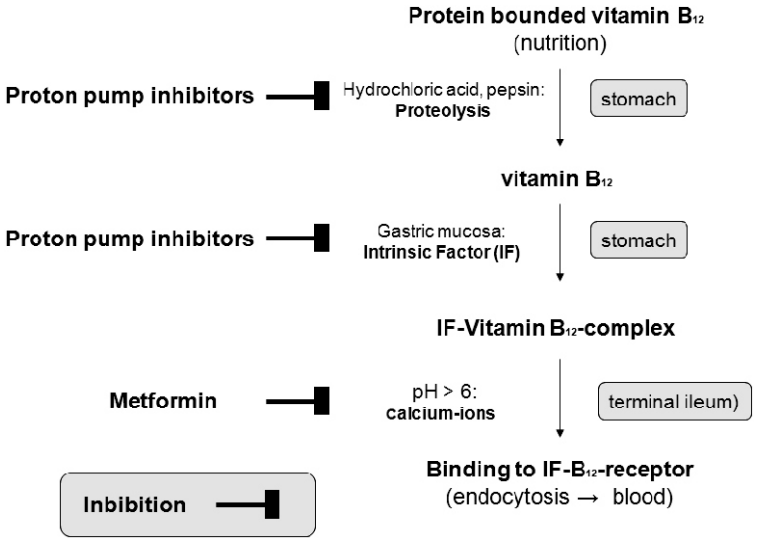

Figure 2. Inhibition of the active absorption of vitamin B12 by proton pump inhibitors and metformin.

nutrient in the gastrointestinal tract, which is most closely associated with pharmacokinetic interactions.

Interactions with absorption

Minerals and antibiotics (Tetracyclines, Gyrase inhibitors)

One of the most frequent causes for therapeutic failure among antibacterials is the intake of tetracyclines (e.g. doxycycline) or gyrase inhibitors (e.g. ciprofloxacin) together with calcium, magnesium, iron and/or zinc (e.g. milk products, mineral nutrients). The formation of poorly absorbable mineral-drug-complexes results in a partial or complete loss of efficiency of the antibiotic. For this reason, the second drug should be taken after a minimum interval of 3 hours.

Fat-soluble vitamins and colestyramine

The anion-exchange resins Colestyramine and Colestipol – used to reduce high cholesterol levels – promote, via the absorption of bile acids the excretion of bile acids and reduce of the hepatic bile acid pool. The new synthesis of bile acids from cholesterol leads to a lower level of cholesterol in the blood. Disorders in the absorption and digestion of fats can result in a lack of fat soluble vitamins (A, D, E, K, Pro-Vitamin A).

In research studies carried out with healthy test people who received 16 g colestyramine on 4 consecutive days, the vitamin B12 absorption dropped by 55 – 90%. Colestyramine becomes bound to the intrinsic factor (IF), thereby affecting the absorption of vitamin B12.

Moreover, the formation of poorly soluble complexes with iron, calcium or magnesium significantly lowers the bioavailability of mineral nutrients.

Vitamin B12 and ulcus drugs (e.g. omeprazole, ranitidine)

Long-term therapies with proton pump inhibitors (e.g. omeprazole) and H2-blockers (e.g. ranitidine) can significantly lower the vitamin B12 serum levels due to reduced vitamin B12 absorption. In our food, vitamin B12 is bound to proteins and is to be released from the binding in the stomach dependent from pH through hydrochloric acid and pepsin. Only then can it become bound to the intrinsic factor in the upper part of the small intestine and absorbed with the help of specific receptors (Figure 2). Up to 40% of elderly people (> 60) suffer from a lack of vitamin B12 as a consequence of atrophic gastritis. In regard to a sufficient supply with vitamin B12, such patients should be given proton pump inhibitors with utmost care.

The inhibition of the intrinsic factor through H2-blockers is of lesser importance for the bioavailability of vitamin B12. What is more important is the risk of pathogenic bacteria populating the gastric mucosa (e.g. Helicobacter pylori) as a consequence of a reduced bactericidal effect of the gastric juice. In addition to vitamin B12 absorption, antacids also decrease the pH-gradient stimulated intestinal absorption of folic acid and thus bioavailability [7].

Biotransformation and metabolism

Vitamin D and anti-epileptics

Anti-epileptics such as phenobarbital, phenytoin, primidone or carbamazepine induce cytochrom-P450-containing mono-oxygenases in the liver catalyze the degradation

Table 5. Bone metabolism disorders caused by anticonvulsants – mechanisms.

– activation (induction) of Cytochrom-P-450 containing mono-oxygenases in the liver that catalyze metabolism and degradation of vitamin D
– increased biliary vitamin D excretion (excretion with bile acids)
– reduced intestinal and renal Calcium absorption (e.g. Phenytoin)
– increased release of Parathormones due to drop of calcium and 25-hydroxy vitamin D3 levels in the serum *(secondary hyperparathyroidism)*
– hypophosphatemia
– increased bone isoenzyme of alkaline phosphatase (bone AP) in the serum
– direct toxic effects (e.g. Carbamazepine, Phenytoin) on osteoblasts
– inhibition of Calcitonine secretion (especially Phenytoin)

and metabolism of vitamin D (Table 5). This results in a significant decrease of the 25-(OH)- and 1.25-(OH)2 vitamin D3 level in the serum and, due to hypocalcemia, to an increase of the parathormone level (secondary hyperparathyroidism). The excretion of pyridinoline crosslinks rises as an indicator for increased bone absorption. Decreasing bone density (lumbar spine L2 – L4) and proliferation of osteocytes are associated with a significantly increased risk of fractures. Pharmacists should therefore inform patients, who regularly take anticonvulsants, about the importance of vitamin D and the individual risk of osteoporosis caused by a lack of vitamin D.

Without adequate substitution of vitamin D, long-term medication with anticonvulsants frequently leads to a lack of vitamin D. Teens who do little physical exercise as well as multiple morbid patients with little exposure to UV light are particularly affected. More often than not epileptic patients consume lots of caffeine-containing drinks (e.g. coffee) due to the side-effects (fatigue) of the drugs, which, however, contribute to a further loss of micronutrients.

Patients with long-term medication of anticonvulsants should be advised to regularly visit their orthopedist to measure bone density (DXA-measuring method) and take an adequate amount of bone-related micronutrients such as vitamin D (1,000 – 2,000 (4,000) i.u./d), calcium and vitamin K, especially during the winter months. Hypovitaminosis D is indicated by a 25-(OH)-vitamin-D3-(calcidiol) serum level of < 80 nmol/l [8].

Vitamin B6 and L-Dopa

The aim of Parkinson's drug therapy is to substitute the missing Dopamine in the central nervous system and mitigate the increased cholinergic activity. The most efficient anti-Parkinson drug to-date is levodopa (L-Dopa) which improves all symptoms of the Parkinson's disease, in particular akinesia and psychic disorders. Since 90% of the orally applied L-Dopa dose is degraded in the periphery so that only 10% is available for the CNS, L-Dopa is almost exclusively used in combination with the decarboxylase inhibitors benserazide or carbidopa. Benserazide and carbidopa inhibit the peripheral decarboxylation of L-Dopa to dopamine and increase the availability of dopamine in the brain. Thanks to this combination, the dose of L-Dopa can be considerably lowered and the peripheral vegetative side-effects reduced.

Higher doses of vitamin B6 (e.g. supplements) can significantly affect the bioavailability and the effectiveness of L-Dopa. Vitamin B6 in the form of pyridoxal-5'-phosphate is a coenzyme of numerous enzymes which play a role predominantly in the amino-acid metabolism. As the coenzyme of L-amino acid decarboxylases, the vitamin accelerates the peripheral decarboxylation of L-Dopa to dopamine. Consequently, the dopaminergic nerve endings in the nigrostriatum have less L-Dopa available, which can be decarboxylated to the active substance dopamine.

Parkinson symptoms such as rigor, akinesia and tremor intensify. Moreover, the un-physiologically high dopamine levels in the periphery lead to gastrointestinal and cardiovascular disorders. Although the combination of L-Dopa with a decarboxylase inhibitor (e.g. carbidopa) mitigates the problematic interaction, patients should not take vitamin B6 in high pharmacological doses (> 10 – 20 mg/day, p.o.) without consulting their physician first!

Excretion

Diuretic therapy will in principle cause a multiple loss of micronutrients, especially of the water-soluble vitamins and minerals, due to renal hyper-excretion.

Magnesium, potassium and diuretics

A major side effect of the thiazide and the high ceiling diuretics is a renal loss of magne-

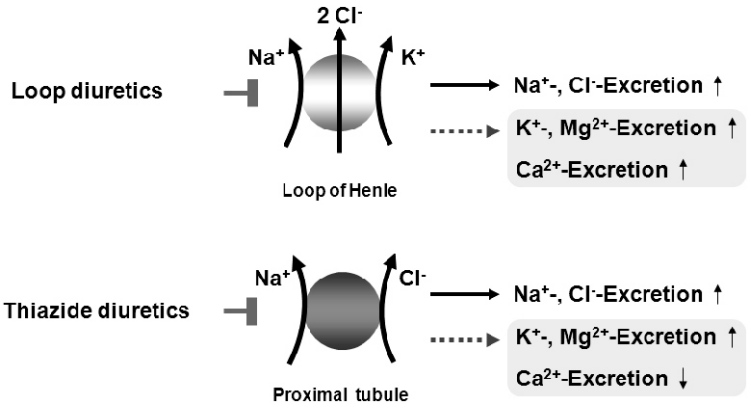

Figure 3. Loop diuretics and thiazides – mechanism of action.

sium and potassium (Figure 3). Magnesium deficiency is a grave problem because magnesium plays a key role in intracellular potassium regulation, and hypomagnesemia can cause cellular potassium depletion. At the same time, magnesium deficiency can cause intracellular sodium and calcium concentrations to rise.

A newly released study on the influence of antihypertensives on magnesium metabolism showed that hypertension patients being treated with anti-hypertensives (for example diuretics, ACE inhibitors or -blockers) were more likely to have a magnesium deficiency than control persons. The compensation of a magnesium deficiency with magnesium supplements led both to a highly significant increase in magnesium blood serum levels and to an average drop in systolic blood pressure by 15 – 20 mm Hg and an average drop in diastolic pressure of 5 – 9 mm Hg. According to reports by patients in this study, the frequency of typical symptoms such as cardiac arrhythmia, angina pectoris sleeping problems and nervousness sank with oral magnesium supplementation (320 mg/d, p.o.).

Magnesium and potassium deficiency are of great clinical significance during long-term treatment with diuretics, because hypomagnesemia and/or hypokalemia can encourage cardiovascular complications (e.g. arrhythmias) and diuretic-associated disturbances of glucose tolerance and lipid metabolism. For this reason, the correction of existing magnesium and potassium deficiencies should be the first step in every hypertension therapy before antihypertensives are administered. Magnesium supplementation can actually reduce the need for antihypertensives and improve cardiac and vascular function in hypertension patients [9].

Vitamin B1 and furosemide

Long-term furosemide therapy for patients suffering from chronic heart failure resulted in thiamine depletion as a consequence of extraordinarily high renal thiamine excretion. According to its physiological importance for energy metabolism, absorption in the gastrointestinal tract vitamin B1 is quickly distributed to the organs and tissues depending on their individual metabolic rate. At 3 – 8 µg/g the myocardium holds the highest proportion of vitamin B1. Thiamine depletion may further deteriorate the cardiac pump function that is already affected by cardiac insufficiency. The thiamine status should be regularly controlled under furosemide therapy (parameter: thiamine level in the blood, transketolase activity) and compensated through substitution with highly bioavailable thiamine derivates (e.g. benfotiamin).

L-Carnitine and Valproic acid

The kidneys play a key role in the homeostasis of the carnitine metabolism. Over 95% of the ultra-filtered carnitine are reabsorbed. The renal clearance of Acylcarnitine is significantly higher (> 3 times) than of free carnitine. Valproic acid binds L-carnitine (valproyl-carnitine) and may result in iatrogenic Carnitine depletion due to increased excretion of valporyl-L-carnitine esters. The -oxidation of fatty acids, i.e. fat burning and energy gain in the form of ATP, is thus disturbed, because fatty acids can only be transported in the form of carnitine esters (Acylcarnitine) through the inner mitochondrial membrane. Valproic acids also affect the cellular carnitine uptake by inhibiting the activity of membrane carnitine transporters, such as carnitine-acylcarnitine translocase (CAT).

Long-term therapy with valproic acid showed that adults, and children in particular, suffer from a lower L-carnitine plasma level, elevated acyl-carnitine: total carnitine ratio in the urine as well as from reduced tubular reabsorption of free L-carnitine in the kidneys. Factors contributing to valproic-acid-induced carnitine depletion are, besides

long-term medication, also combination therapies with other anti-epileptics (phenobarbital, phenytoine). Patients, who are treated with the anti-epileptic valproic acid over a long period, may benefit from carnitine supplements (500 bis 1,000 mg/d, p.o.) [10].

L-Carnitine and cisplatin

The carnitine system undergoes several modifications in tumor diseases and in experimental tumor models. Notably, some antineoplastic drugs, produce adverse effect of derogating this system. This is the case with cisplatin, ifosfamide and adriamycin. Cisplatin increases the renal excretion of carnitine by the factor 10, probably due to tubular damage and inhibition of carnitine Reabsorption. Patients receiving cisplatin need a replacement therapy with L-carnitine (e.g. 1,000 mg L-carnitine/d, p.o.) and magnesium to avoid or minimize magnesium and carnitine deficiency and metabolic disturbances. A metabolite of ifosfamide, chloroactealdehyde, promotes carnitine deficiency and seems to be responsible for side effects of this antineoplastic drug. Supplementation with carnitine could be beneficial to patients treated with ifosfamide, due to the role of carnitine in the detoxification of chloroacetaldehyd [1, 11].

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