J. Elem. s. 127–134 DOI: 10.5601/jelem.2013.18.1.11

ANTIHYPERTENSIVE DRUGS AFFECT POTENTIAL BIOAVAILABILITY OF MINERALS FROM SHELLED PEA

Joanna Sulibursk[1], Paweł Bogdanski[2], Barbara Chiniewicz

[1]Chair of Hygiene and Human Nutrition
Poznan University of Life Sciences
[2]Department of Internal Medicine, Metabolic Disorders and Hypertension
University of Medical Science in Poznan

Abstract

Interaction of antihypertensive drugs with minerals can occur during digestion in the digestive tract of patients. The aim of this study was to estimate the influence of hypotensive drugs on the bioavailability of magnesium, iron, zinc and copper from shelled pea during *in vitro* enzymatic digestion.

The degree of release of magnesium, iron, zinc and copper from shelled pea was determined with and without (the control) addition of hypotensive drugs. Four antihypertensive drugs in standard doses (one tablet per sample) were analysed: Metocard (β-blocker), Cardilopin (Ca-antagonist), Apo-perindox (angiotensin-converting-enzyme inhibitor ACE-I) and Indapen (diuretic). The samples were subjected to enzymatic digestion under *in vitro* conditions. The content of minerals in shelled pea before and after enzymatic digestion was determined by flame atomic absorption spectrometry (AAS).

It was found that Indapen (indapamide) significantly decreased the release of magnesium, iron and zinc from shelled pea. The degree of release of magnesium was lower in samples with Metocard (metoprolol) than in the control. The release of copper was significantly reduced by Cardilopin (amlodipine).

Indapamide, metoprolol and amlodypine decreased the release of minerals from pea *in vitro* enzymatic digestion of shelled pea.

Key words: food-drug interaction, mineral bioavailability.

Joanna Sulibursk, PharD, Chair,of Hygiene and Human Nutrition, Poznan University of Life Sciences, Wojska Polskiego 31, 60-624 Poznan, Poland, phone: +48(0)61 84 87 334, e-mail: jsulibur@up.poznan.pl

WPŁYW WYBRANYCH LEKÓW HIPOTENSYJNYCH NA BIODOSTĘPNOŚĆ SKŁADNIKÓW MINERALNYCH Z GROCHU ŁUSKANEGO W PROCESIE TRAWIENIA ENZYMATYCZNEGO *IN VITRO*

Abstrakt

Podczas trawienia może dojść do interakcji między lekami hipotensyjnymi a składnikami mineralnymi w przewodzie pokarmowym pacjentów. Celem pracy było określenie wpływu leków hipotensyjnych na biodostępność magnezu, żelaza, cynku i miedzi z grochu łuskanego w warunkach trawienia enzymatycznego *in vitro*.

Stopień uwolnienia magnezu, żelaza, cynku i miedzi z grochu łuskanego oceniano w próbkach z dodatkiem i bez dodatku (próba kontrolna) leków hipotensyjnych. Analizowano cztery leki hipotensyjne w dawkach standardowych (jedna tabletka w próbie): metocard (β-bloker), cardilopin (antagonista wapnia), apo-perindox (inhibitor konwertazy angiotensyny (ACE-I)) i indapen (diuretyk). Próbki poddano trawieniu enzymatycznemu w warunkach in vitro. Zawartość składników mineralnych w grochu łuskanym przed i po trawieniu enzymatycznym określono za pomocą spektrofotometrii atomowo-absorpcyjnej (AAS).

Stwierdzono, że indapen (indapamid) istotnie zmniejszył uwalnianie magnezu, żelaza i cynku z grochu łuskanego. Stopień uwalniania magnezu był niższy w próbkach z metocardem (metoprolol) niż w próbkach kontrolnych. Uwalnianie miedzi było istotnie mniejsze pod wpływem cardilopinu (amlodypina).

Indapamid, metoprolol i amlodypina zmieniają stopień uwolnienia składników mineralnych z grochu łuskanego w procesie trawienia enzymatycznego *in vitro*.

Słowa kluczowe: interakcje żywność-lek, biodostępność składników mineralnych.

INTRODUCTION

Disorders in the mineral budget of patients with hypertension have been observed in several studies (Kesteloot et al. 2011, Suliburska et al. 2011b). It is known that many nutritional and non-nutritional factors influence absorption of minerals from food, their excretion and metabolism. Both *in vitro* and *in vivo* studies show that bioavailability of minerals depends on the food content of various antinutrients, such as oxalic acid, phytates, dietary fibres and polyphenols, which act as mineral binders or chelators (Oatway et al. 2001, Sandberg 2002, Skibniewska 2002). The degree of mineral release from food products also depends on the processing technology (Suliburska et al. 2009a)

Experimental results show that drugs can also affect the mineral status in patients. Hypotensive drugs influence specially the levels of magnesium, potassium, sodium and calcium in the organism. Treatment with ACE-I and loop diuretics results in a decrease in the serum concentration of magnesium and high losses of this element with urine. However, it has also been shown that lisinopril saves magnesium in patients with congestive heart failure (Oladapo, Falase 2000). It was found that thiazides had a beneficial effect on calcium metabolism in elderly individuals (Ott et al. 2008). Golic

et al. (1998) found that treatment of hypertensive patients with captopril or enalapril may result in zinc deficiency.

Interaction of antihypertensive drugs with minerals can occur during digestion in the digestive tract of patients. The aim of this study was to estimate the influence of selected hypotensive drugs on the bioavailability of magnesium, iron, zinc and copper from shelled pea during *in vitro* enzymatic digestion.

MATERIAL AND METHODS

Food sample

The experimental material was shelled pea, purchased on the local market (the city of Poznan, 2010). Food samples were ground in an electrical mill under laboratory conditions and passed through sieves to divide into fractions with particles having the maximum diameter of less than 2 mm. Samples were dried at 105ºC.

Drugs

In the experiment, four antihypertensive drugs were used: Metocard (β-blocker), Cardilopin (Ca-antagonist), Apo-perindox (ACE-I) and Indapen (diuretic). Characteristics of the drugs are shown in Table 1.

Table 1

Characteristics of the drugs

Drug	Active substance	Dose of active substance (mg/1 tablet)	Antihypertensive - drug class
Metocard	metoprolol	47.5	β-blocker
Cardilopin	amlodipine	10.0	Ca-antagonist
Apo-Perindox	perindopril	3.34	ACE inhibitor
Indapen	indapamide	1.5	diuretic

Enzymatic digestion

Samples were divided into five groups: the control, Metocard, Cardilopin, Apo-perindox and Indapen. The control samples comprised only the product without any drugs. One tablet of a given drug was added the other samples.

In vitro enzymatic digestion was performed according to SKIBNIEWSKA et al. (2010). In the experiment, one dose of each drug (equivalent of 1 tablet) was analyzed. Each tablet of a given drug was crushed in a mortar and

mixed with a sample (2 g) of finely ground shelled pea in conical beakers, filled with deionised water (20 ml) and shaken for 10 min. In order to create suitable conditions for pepsin activity, pH was brought to 2 using 0.1 M HCl aqueous solution (Suprapure, Merck). Afterwards, pepsin solution (0.5 ml 100 ml^{-1}) was added to the homogenate. Next, the samples were placed in a thermostat shaker (37°C) for 2 hours. During the incubation, pH was maintained or corrected by addition of 6 M HCl aqueous solution whenever necessary. After 2 hours, the digested samples were treated with 6% $NaHCO_3$ aqueous solution (Extrapure, Merck) to bring pH to 6.8-7.0, subjected to pancreatin solution (10 ml/40ml of homogenate) and placed in a thermostatic shaker (37°C) for 4 hours. Afterwards, the digested samples were centrifuged for 15 min (4000 rpm min^{-1}) and clear solution was quantitatively transferred to quartz crucibles, where it was treated with a mixture of concentrated nitric (65% w/w) and perchloric (70% w/w) acids (2:1 v/v) (Suprapure, Merck). The samples were placed in a thermostatic block and heated until complete mineralization.

Control samples were also prepared, in which the product was digested without any addition of the drugs. For each drug, a reagent sample was made, which contained one tablet of a given drug and reagents. All samples were subjected to enzymatic digestion.

In order to determine the total content of minerals in native products, food samples (2 g) were ashed in a muffle furnace at 450°C until complete mineralization and then dissolved in 1N nitric acid. All samples were analyzed in triplicate.

Determination of minerals

The content of minerals in native, *in vitro* digested food products (with and without drugs) was determined by atomic absorption spectrometry (AAS-3, Zeiss spectrometer) with air-acetylene flame, after diluting each sample adequately with deionized water (for Fe, Zn, Cu) or with LaCl3 (0.3% solution, for Mg). The methods were validated by simultaneous assays of the reference material (Soya Bean Flour, INCT-SBF-4), at the accuracy 93.1%, 97.2%, 94.5% and 103.1% for Mg, Fe, Zn and Cu, respectively. The content of minerals in food products was expressed in mg 100 g^{-1} dry mass, while the degree of release for a mineral (its potential bioavailability) was expressed as a percentage of the mineral released vs its total content.

Statistical analysis

The experimental results were given as means ± SD of three parallel measurements. The statistical analysis was carried out using Statistica 7.0 software and Anova was performed at the significance level α=0.05.

RESULTS AND DISCUSSION

Table 2 shows the total content of minerals in shelled pea. This table also presents the amount of minerals (mg) released from 100 g of products (the control sample). This index may reflect their potential bioavailability.

Table 2

Content of minerals in shelled pea and amount released in digestion process (mg 100 g^{-1} d.w.).

Parameters	Mg	Fe	Zn	Cu
Content	90.2±0.6	3.37± 0.03	5.66± 0.03	0.67±0.01
Amount released	85.6±0.5	1.07±0.03	2.75±0.01	0.60±0.01

Table 3 presents the degree of release of minerals in samples with or without the drugs. In some cases, the analysed drugs affected the degree of release of minerals from pea. It was found that Indapen caused a markedly lower release of magnesium, iron and zinc from shelled pea when compared with the control sample. The amount of available copper was significantly lower in samples with Cardilopin than in samples without any drugs. Moreover, Metocard markedly reduced the release of magnesium from the product. Apo-perindox did not affect the release of analysed minerals from shelled pea.

Like all chemical compounds, pharmaceuticals may interact with nutrients. These interactions can lead to reduced or increased release of minerals from food and may affect the bioavailability of minerals.

ACE inhibitors, e.g. captopril and enalapril, have functional groups such as sulphydryl groups or carboxyl groups, whose capacity for binding zinc determines the mineral status of the organism (Golik et al. 1998). Angiotensin converting enzyme inhibitors bind metal ions (iron, copper and zinc) and through this mechanism drugs may interfere with metal-catalyzed reactions (free radical generation) or metal absorption and excretion (Fernandes et al. 1996, Leary et al. 1992). In our previous study, we observed some interaction between perindopril and magnesium and iron (Suliburska et al. 2011a). Contrary to that finding, in the present experiment, perindopril did not markedly affect the release of minerals from shelled pea.

In this study, metaprolol decreased the concentration of magnesium in the supernatant after digestion. No information was found in literature which would indicate direct interaction between metoprolol and magnesium or other elements. However, another β-blocker – carvedilol – is a metal chelator and exhibits antioxidant activity (Oettl et al. 2001). It was also found that propranolol (a β-blocker) and verapamil (a Ca-antagonist) have significant inhibitory impact on peroxidation in tissues in the presence of iron ions (Aruoma et al. 1991).

Table 3

Influence of antihypertensive drugs on release of minerals during digestion

Samples	Mg (%)		Fe (%)		Zn (%)		Cu (%)	
Control	94.9±3.5^{b}	-	31.6±1.3^{b}	-	48.6±3.2^{b}	-	90.0±3.2^{b}	-
Metocard (β-bloker)	57.9±0.8^{a}	(-)39.0*	31.6±1.6^{b}	(-)0.2*	49.1±0.2^{b}	(+)1.0*	85.2±3.2^{ab}	(-)5.3*
Cardilopin (Ca-antagonist)	96.1±0.4^{b}	(+)1.3*	39.0±0.6^{b}	(+)3.3*	49.6±0.1^{b}	(+)1.9*	77.2±2.1^{a}	(-)14.3*
Apo-Perindox (ACE-inhibitor)	93.4±0.4^{b}	(-)1.6*	33.4±0.4^{b}	(+)5.6*	51.8±0.1^{b}	(+)6.6*	96.0±1.1^{b}	(+)6.7*
Indapen (diuretic)	43.1±0.3^{a}	(-)54.6*	16.1±0.2^{a}	(-)49.0*	36.4±0.5^{a}	(-)25.2*	88.5±1.8^{b}	(-)1.6*

*+/– degree of released minerals compared with control sample
a,b - significant differences; $p<0.05$

Several studies have shown that administration of indapamide is associated with hyponatremia and other electrolytic disorders, especially hypomanesemia and depressed zinc in the organism (KHEDUN et al. 1995, PAK 2000, YONG et al. 2011). It is known that indapamid forms complexes with copper when the conditions are suitable (RADI 2003). Under the *in vitro* digestion performed in this study, indapamid did not result in the release of copper, but decreased the release of the other minerals, i.e. magnesium, zinc and iron. In our previous study, indapamid affected potential bioavailability of copper from buckwheat (SULIBURSKA et al. 2011a). Moreover, in another experiment we found out that amlodipin and indapamid induced an evident increase in the activity of pepsin (SULIBURSKA et al. 2009a). Higher activity of digestive enzymes can influence the release of minerals from complexes with other components in shelled pea. Both Cardilopin (amlodipine) and Indapen (indapamid) significantly decreased the release of some minerals from the product.

These differences, observed in our previous and the present experiments, may have been caused by the fact that buckwheat groats and pea differ significantly in terms of their composition. Pea contains much more proteins and fiber but less fat than buckwheat groats (PERIAGO et al. 1998, CHRISTA, SORAL-ŚMIETANA 2008). Individual ingredients in a product may interact with drugs, thus affecting the release of minerals. Moreover, the differences in the results from our experiments on buckwheat and pea may be due to their effect on pH. Buckwheat is acidic and this can enhance the effects of indapamine and amlodipine on pepsin. In contrast, pea is alkaline and the effect of these drugs on pepsin in its presence could be weakened.

CONCLUSIONS

1. Indapamide, amlodipine and metoprolol affected the release of magnesium, iron, zinc and copper from shelled pea in vitro enzymatic digestion.

2. Hypotensive drugs may diminish the potential bioavailability of minerals.

REFERENCES

ARUOMA O.I., SMITH CH., CECCHINI R., EVANS P.J., HALLIWELL B. 1991. *Free radical scavenging and inhibition of lipid peroxidation by β-blockers and by agents that interfere with calcium metabolism: A physiologically-significant process*? Biochem. Pharm., 42(4): 735-743.

CHRISTA K. SORAL-ŚMIETANA M. 2008. *Buckwheat grains and buckwheat products – nutritional and prophylactic value of their components – a review.* Czech J. Food Sci., 26(3): 153-162.

FERNANDES A.C., FILIPE P.M., FREITAS J.P., MANSO C.F. 1996. *Different effects of thiol and non thiol ACE inhibitors on copper induced lipid and protein oxidative modification.* FRBM, 20(4): 507-514.

Golik A., Zaidenstein R., Dishi V., Blatt A., Cohen N., Cotter G., Berman S., Weissgarten J. 1998. *Effects of captopril and enalapril on zinc metabolism in hypertensive patients*. J. Am. Coll. Nutr., 17(1): 75-78.

Kesteloot H., Tzoulaki I., Brown I.J., Chan Q., Wijeyesekera A., Ueshima H., Zhao L., Dyer A.R., Unwin R.J., Stamler J., Elliott P. 2011. *Relation of urinary calcium and magnesium excretion to blood pressure: The international study of macro- and micronutrients and blood pressure and the international cooperative study on salt, other factors, and blood pressur*e. Am. J. Epidemiol., 174(1): 44-51.

Khedun S.M., Naicker T., Maharaj B. 1995. *Zinc, hydrochlorothiazide and sexual dysfunction*. Cent. Afr. J. Med., 41(10): 312-315.

Leary W.P., Phil D., Reyes A.J., Van Der Bryl K. 1992. *Effects of angiotensin-converting enzyme inhibitors on urinary excretions: interactions with diuretics*. Am. J. Med., 92(4): 64-68.

Oatway L., Vasanthan T., Helm J.H. 2001. *Phytic acid*. Food Rev. Inter., 17: 419-431.

Oettl K., Greilberger J., Zangger K., Haslinger E., Reibnegger G., Jurgens G. 2001. *Radical-scavenging and iron-chelating properties of carvedilol an antihypertensive drug with antioxidative activity*. Biochem. Pharmacol., 62: 241-248.

Oladapo O.O., Falase A.O. 2000. *Serum and urinary magnesium during treatment of patients with chronic congestive heart failure*. Afr. J. Med. Med. Sci., 29(3-4): 301-303.

Ott S.M., LaCroix A.Z., Scholes D., Ichikawa L.E., Wu K. 2008. *Effects of three years of low-dose thiazides on mineral metabolism in healthy elderly persons*. Osteoporos. Int., 19(9): 1315-1322.

Pak C.Y. 2000. *Correction of thiazide-induced hypomagnesemia by potassium-magnesium citrate from review of prior trials*. Clin. Nephrol., 54(4): 271-275.

Periago M.J., Vidal M.L., Ros G., Rincon F., Martinez C., Lopez G., Rodrigo J., Martinez I. 1998. *Influence of enzymatic treatment on the nutritional and functional properties of pea flour*. Food Chem., 63(1): 71-78.

Radi A. 2003. *Adsorptive cathodic stripping voltammetric determination of indapamide as copper complex at a hanging mercury drop electrode*. Chem. Anal., 48(2): 273-281.

Sandberg A.S. 2002. *Bioavailability of minerals in legumes*. Br. J. Nutr., 88: 281-285.

Skibniewska K., Kozirok W., Fornal L., Markiewicz K. 2002. *In vivo availability of minerals from oat products*. J. Sci. Food Agric., 82: 1676-1681.

Skibniewska K.A., Zakrzewski J., Siemianowska E., Polak-Juszczak L., Aljewicz M. 2010. *Calcium availability from yogurt by itself or yogurt-cereal-containing products*. J. Toxicol. Environ. Health A., 73(17-18): 1150-1154.

Suliburska J., Bogdański P., Krejpcio Z., Pupek-Musialik D. 2009a. *The influence of perindopril, amlodipine and indapamide on in vitro pepsin activity*. Farm. Współ., 2: 171-174. (in Polish)

Suliburska J., Krejpcio Z., Lampart-Szczapa E., Wójciak R.W. 2009b. *Effect of fermentation and extrusion on the release of selected minerals from lupine grain preparations*. Acta Sci. Pol. Technol. Aliment., 8(3): 87-96.

Suliburska J., Bogdański P., Chiniewicz B. 2011a. *The influence of selected hypotensive drugs on the bioavailability of minerals from buckwheat groats in vitro enzymatic digestion*. Acta Sci. Pol. Technol. Aliment., 10(4): 507-513.

Suliburska J., Bogdanski P., Pupek-Musialik D., Krejpcio Z. 2011b. *Dietary intake and serum and hair concentrations of minerals and their relationship with serum lipids and glucose levels in hypertensive and obese patients with insulin resistance*. Biol. Trace Elem. Biol., 139: 137-150.

Yong T.Y., Huang J.E., Li J.Y. 2011. *Severe hyponatremia and other electrolyte disturbances associated with indapamide*. Curr. Drug Saf., 6(3): 134-137.