SHORT COMMUNICATION

Decreased consumption of corticosteroids after selenium supplementation in corticoid-dependent asthmatics

Gazdik F, Kadrabova J, Gazdikova K

*Institute of Preventive and Clinical Medicine, Department of Clinical Immunology, Bratislava, Slovak Republic.***gazdik@upkm.sk**

Abstract

Selenium represents a trace element comprised in enzyme glutathion-peroxidase. It is anti-inflammatory activity is based on the elimination of hydroperoxides produced in the site of inflammation (scavenger of free oxygen radicals). The authors report the results of a pilot study with 17 corticodependent asthmatics (7 females, 10 males) aged 30 - 74 years, supplemented with the preparation of selenium (Se), in a daily dose of 200 µg during the follow-up lasting 96 weeks. We demonstrate the reduced consumption of both inhaled corticosteroids, manifested after 24 to 96 weeks of Se supplementation (SeS) (21.74 mg vs 15.81 mg, p<0.009, 21.74 mg vs 15.32 mg, p<0.007, respectively) and systemic corticosteroids after 48 weeks (294 mg vs 78 mg, p<0.04) and 96 weeks of SeS (294 mg vs 104 mg, p<0.04). These results correlated with the elevation of Se levels both in plasma and erythrocytes (p<0.0003, p<0.0003, respectively). No adverse effects were seen during the study and the tolerance of preparation was good. ***(Tab. 3, Ref. 17.)***

Key words: corticoid-dependent asthmatics, inhaled and systemic corticosteroids, supplementation of selenium.

Selenium (Se) is a trace element that was discovered by Jons Jacob Berzelius in 1817. In humans it is dominantly comprised in enzyme glutathione-peroxidase (Gpx) and represents a component of both intracelullar and membrane antioxidant defence systems.

Gold standard of therapeutic approach in asthma bronchiale (AB) represents the administration of corticosteroids (CS). In clinical practice, CS inhalation, with topical route of application is preferred. These formulas are characterised by less frequent manifestations of adverse reactions in comparison with systemic CS, but, however their total elimination could not be excluded.

In 1996, Kadrabová et al. published the results of suboptimal Se status of asthmatics in the region of Bratislava (Kadrabová et al, 1996). The Se deficiency could be caused by a decreased intake in food or by elevated consumption in process of chronic inflammation due to Se Gpx activity (eradication of free oxygen radicals, scavenger activity).

In the presented study we have postulated the thesis of optimal Se status corrected by Se supplementation (SeS) that could have led to the attenuation of the inflammatory process in bronchi followed by a decrease in consumption of CS in corticoid-dependent asthmatics (CDAs).

Aims

The aims of the study were to evaluate the effects of SeS on Se status in CDAs in respect of CS consumption and the functional spirometric parameters. The compliance of patients, tolerance and manifestation of adverse reactions during SeS were also observed.

Patients and methods

Seventeen CDAs (7 females and 10 males) aged from 30 to 74 yrs (average age 55 yrs) were enrolled into the pilot open clinical study. All of the patients participating in the study fulfilled the criteria of asthma as recommended by the American Thoracic Society published in the year 1987 (American Thoracic

Institute of Preventive and Clinical Medicine, Department of Clinical Immunology, Bratislava, Slovakia

Address for correspondence: F. Gazdik, MD, PhD, Institute of Preventive and Clinical Medicine, Department of Clinical Immunology, Limbova 14, SK-833 01 Bratislava 37, Slovakia.
Phone: +421.2.59369401

Society, 1987). Inhaled CS (beclomethasone dipropionas) were administered. Four asthmatics also used systemic CS (methylprednisolon). The asthmatics with suboptimal Se levels in plasma (with values on lower, or below the reference range) were included into the study.

Selenium supplementation

The SeS has been done by preparation Selenium during 96 weeks of follow up, in the total daily dose of 200 µg (2x2 tablets daily, each tablet contained 50 µg of Se).

The arrangement of the study

The study has been performed in form of pilot, simple and opened clinical trials. During the period of 4 weeks before SeS we had assessed the total consumption of CS in doses in order to ensure the optimal functional spirometric parameters in probands. The efficacy of anti-inflammatory therapy has been determined by the reversibility of chronic obstructive disorder (reversibility of bronchial obstruction after administration of ß-agonist under the standard conditions (salbutamol, preparation Ventolin spray).

The bronchodilatating test was performed by inhalation of two doses of Ventolin spray, followed by the measurement of spirometric parameters after 30 minutes of administration T-tests being done by a spirometric machine (Ganshorn, Germany) during the period from 8 to 10 o'clock a.m. Before the performance of functional spirometric tests, the asthmatic patients had not used the morning dose of ß-agonist at home. Before the period of SeS (-4 weeks) and in the following periods of SeS (4th, 8th, 12th, 24th, 48th, 72nd and 96th weeks) the total consumption of CS was calculated (the total consumption of CS during the period of 4 weeks). Functional spirometric tests were done in the following periods: -4th, 12th, 24th, 48th, 72nd and 96th weeks of the observation. From the 12th week on we gradually reduced the CS therapy in the dependence on the functional spirometric results and clinical status of patients. The levels of Se in plasma and erythrocytes were assessed in intervals identical with those used in functional tests. Continous flow vapor system PU 9360 connected with PU 9200 atomic absorption spectrophotometer (Unicam Analytical Systems) was used for the determination of Se in plasma and erythrocytes after wet digestion of samples. To ensure the accuracy of Se determination, the standard serum (Seronom Trace Elements, Nycomed, Norway) and bovine liver (No. 12-2-01, Institute of Metrology, Slovakia) were simultaneously measured. Good accordance was achieved between both the determined and referenced values (Kadrabová, 1996).

Tab. 1. The level of Se in plasma and in erythrocytes (ng/ml) (n=17).

	Week					
	-4	**12**	**24**	**48**	**72**	**96**
Se in plasma	59,13±	101,16	102,7	111,94	116,04	109,9
±SEM	± 1,60	2,21	2,02	3,46	5,32	2,69
p		0,0003	0,0003	0,0003	0,0003	0,0006
Se in erythrocytes	281,7	335,76	360,18	403,82	388,94	411,93
±SEM	7,64	9,7	10,06	16,43	10,40	11,08
p		0,0003	0,0003	0,0003	0,0003	0,0006

Notes: No — number of patients, Se — selenium, SEM — standard error mean, p — statistical significance

The statistical evaluation

The statistical evaluation was done by pair Wilcoxon's test. The data were analyzed and expressed as the standard mean error. p-Values less than 0.05 were regarded as significant.

Results

Levels of Se elevated significantly both in plasma and erythrocytes already after the 12th week of SeS ($p<0.0003$, $p<0.0003$). Increased levels were in the reference range and persisted until the 96th week of SeS ($p<0.0006$, $p<0.0006$) (Tab. 1).

The consumption of inhaled CS gradually reduced since the 12th week (Tab. 2) but a statistically significant reduction appeared from the 24th week on and persisted until the 96th week of SeS (21.74 mg vs 15.81 mg, 21.74 mg vs 15.32 mg, $p<0.009$, $p<0.007$, respectively) (Tab. 2).

The consumption of systemic CS reduced significantly after the 48th week of SeS and persisted also in the 96th week of SeS

Tab. 2. Consumption of inhaled corticosteroids (CS) - beclomethason dipropionas (mg) (n=17) and systemic CS - methyprednisolon (mg) (n=4) per 4 weeks.

	Week						
	-4-0	**8-12**	**20-24**	**30-36**	**44-48**	**68-72**	**92-96**
Inhaled CS	21,74	16,81	15,81	14,82	13,51	12,02	15,32
±SEM	2,75	2,67	2,21	1,86	2,31	2,03	2,40
p		NS	0,009	0,001	0,0009	0,0006	0,007
Systemic CS	294	118	132	168	78	128	104
±SEM	128	42,8	44,4	100	41,7	61,4	39
p		NS	NS	NS	0,04	NS	0,04

Notes: No — number of patients, SEM — standard error mean, p — statistical significance, CS — corticosteroids

Tab. 3. Spirometric parameters (n=17).

	Week						
	-4	**12**	**24**	**36**	**48**	**72**	**96**
ΔFVC (%)	9,88	7,71	10,24	10,00	14,94	10,00	7,94
±SEM	2,61	3,08	2,92	2,00	3,13	2,19	4,38
p		NS	NS	NS	NS	NS	NS
ΔFEV_1 (%)	17,94	15,89	18,53	19,94	25,41	15,82	19,6
±SEM	2,21	2,53	2,97	2,61	4,26	2,14	4,12
p		NS	NS	NS	NS	NS	NS
ΔFEV_1/FVC (%)	7,41	8,12	8,82	9,0	8,94	5,53	11,06
±SEM	1,91	2,08	1,30	2,13	2,21	1,63	3,61
p		NS	NS	NS	NS	NS	NS
ΔMEF 50 (%)	39,18	46,41	44,24	49,18	57,35	36,24	47,50
±SEM	6,01	11,67	8,31	8,33	9,41	6,05	8,18
p		NS	NS	NS	NS	NS	NS
ΔMEF 25 (%)	30,82	45,76	37,88	41,41	36,88	32,59	24,56
±SEM	9,62	8,41	9,36	5,60	8,91	7,26	9,02
p		NS	NS	NS	NS	NS	NS
ΔPEF (%)	18,82	15,76	21,06	22,06	33,53	16,18	23,75
±SEM	4,19	3,95	4,71	4,96	5,55	2,79	4,70
p		NS	NS	NS	0,02	NS	NS

Notes: No — number of patients, ΔFEV_1 — the change (delta) in forced expiratory flow per 1st second after bronchodilatating test, ΔFEV_1/FVC — the change (delta) in ratio in forced expiratory flow per 1st second to forced vital capacity after bronchodilatating test, ΔFVC — the change (delta) in forced vital capacity after bronchodilatating test, ΔMEF50 — the change (delta) in flow in 50 % of FVC after bronchodilatating test, ΔMEF25 — the change (delta) in flow in 25 % of FVC after bronchodilatating test, ΔPEF — the change (delta) in peak expiratory flow, SEM — standard error mean, p — statistical significance

(294 mg vs. 78 mg, 294 vs 104 mg, $p<0.04$, $p<0.04$, respectively) (Tab. 3). The correlation between the elevation of Se both in plasma and erythrocytes and the reduction of CS consumption was evident whereas spirometric parameters did not change significantly in comparison with the period before SeS (-4th week) (Tab. 3).

The parameter of peak expiratory flow had the tendency to elevate but a significant elevation was noticed only after the 48th week of SeS ($p<0.02$) (Tab. 3).

The compliance of the patients during the study was very good. It has been confirmed by significantly increased levels of Se in plasma and erythrocytes since the 12th week of SeS, and the elevation persisted during the whole observed periods of the study.

Discussion

The significance of Se in antioxidative defence system is generally well known. In humans, Se is comprised dominantly in enzyme Gpx that represents antioxidative effects.

One of the relevant activities of Se-Gpx may reside in its ability to catalyse the reduction of hydroperoxides by glutathione, and in this way to protect the biomembranes from the oxidative breakdown caused by oxygen radicals. Another possible mechanism may act through its effects in the regulation of cellular proxide levels, and therefore indirectly in that of eicosanoid production from arachidonic acid via the lipoxygenase and cyclo-oxygenase pathways. Oxygen radicals may also react with a component of plasma to form a product that is chemotactic for neutrophils, and increase capillary wall permeability. The secretion of toxic oxidants may also contribute to tissue injury in the lung by oxidative inactivation of protective anti-proteases (Beasley et al, 1991).

AB represents a chronic inflammatory disease the pathogenesis of which is of multi-factorial nature. The participation of free oxygen radicals produced in sites of inflammation (mucosa of bronchi) is also accepted (Beasley et al, 1991). Several authors reported results of decreased Se status, which correlated with the decreased activity of Se Gpx in asthmatics (Flatt et al, 1990; Hasselmark et al, 1990; Hasselmark et al, 1993; Miss et al, 1996; Pearson et al, 1991; Stone et al, 1989). We also demonstrated the decreased status of Se in asthmatics from the region of Bratislava (Kadrabová et al, 1996). It is assumed that the decreased status of Se represents one of the risk factors of developing AB (Flatt et al, 1990; Shaw et al, 1994; Jones et al, 1987). In this respect, we postulated a thesis that optimal SeS, by enhancing the eradication of free oxygen radicals through the activity of enzyme Se Gpx could lead to sparing effects of CS consumption.

In the presented study we have noticed subpoptimal Se levels (below or on the lower level of the reference range) in CDAs. In this respects the published data are controversial. Some authors have reported increased levels of Se in plasma in CDAs (Fenech

et al, 1998; Marano et al, 1990), but the others did not observe the differences in plasma levels and the activity of Gpx (Flatt et al, 1990).

The main message of the presented study is to answer the questions as to whether the SeS can reduce the consumption of CS in CDAs. The comparison of consumption before and after SeS confirmed the significant reduction of both inhaled and systemic CS. We found the correlation between the rise of Se levels in plasma and erythrocytes and the reduction of CS consumption without any significant changes in spirometric parameters. The persistence of reversibility of the obstructive disorder represented the objective criterion for judging the efficacy of reduced CS therapy.

The current therapeutic strategy trends to use the combination of preparation with anti-inflammatory effects to reduce manifestations of adverse reactions. A long-term treatment with high doses of inhaled CS may be accompanied by manifestations of adverse reactions, such as candidosis of mucosa observed in esophagus and mouth, dysphonia, eye complications (glaucoma and cataracta), respiratory oportunistic infections, disorders of bone metabolism (slow growth of bones) (Autio et al, 1996; Mak et al, 1992).

The SeS in the daily dose of 200 g during the period of 96 weeks significantly elevated the levels of Se both in plasma and erythrocytes from the 12th week of the follow up. It is evident that bioavailability of preparation was good. The current monitoring of Se levels during the study demonstrated good compliance of patients. The tolerance of the preparation was very good and no adverse reactions were seen.

The results of the presented pilot study demonstrated suboptimal levels of Se in plasma and erythrocytes in CDAs. After SeS, the levels of Se significantly increased and were accompanied by a significant reduction in inhaled and systemic CS. It is important to emphasize that the reversibility of obstructive disorder in bronchi has been well preserved although the reduction of CS therapy has been performed. In the daily dose of 200 μg of Se during the period of 96 weeks the compliance of patients was good and no adverse reactions occured.

We presented the results of a pilot opened clinical trial. In future, controlled double-blinded study is required to perform.

References

American Thoracic Society: Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Amer Rev Resp Dis 1987; 136: 228—231.

Autio P, Karjalainen J, Risteli L et al: Effects of an inhaled steroids (budesonide) on skin collagen synthesis of asthma patients in vivo. Amer J Resp Crit Care Med 1996; 153: 1172—1175.

Beasley R, Thomson C, Pearce N: Selenium, glutathione peroxidase and asthma. Clin Exp Allergy 1991; 21: 157—159.

Fenech AG, Ellul-Micallef R: Selenium, glutathione peroxidase and superoxide dismutase maltese asthmatics patients: effect of glucocorticoid administration. Pulm Pharmacol Ther 1998; 11 (4): 301—308.

Flatt A, Pearce N, Thomson CD, Sears MR, Robinson MF, Beasley R: Reduced selenium in asthmatic subjects in New Zealand. Thorax 1990; 45 (2): 95—99.

Hasselmark L, Malmgren R, Unge G, Zetterstrom O: Lowered platelet glutathione peroxidase activity patients with intrinsic asthma. Allergy 1990; 45: 523—527.

Hasselmark L, Malmgren R, Zetterstrom O, Unge G: Selenium supplementation in intrinsic asthma. Allergy 1993; 48 (1): 30—36.

Jones DT, Sears MR, Holdaway MD, Hewitt CJ, Flannery EM, Herbison GP, Silva PA: Childhood asthma in New Zealand. Brit J Dis Chest 1987; 81: 332—340.

Kadrabová J, Maďarič A, Ginter E: Suboptimálny status selénu u populácie v bratislavskom regióne. Clin Biochem Metabol 1995; 3 (24): 175—177.

Kadrabová J, Maďarič A, Kováčiková Z, Podivinský F, Ginter E, Gazdík F: Selenium status is decreased in patients with intrinsic asthma. Biol Trace Elem Res 1996; 52: 241—248.

Mak VHF, Melchor R, Spiro SG: Easy brusing as a side-effect of inhaled corticosteroids. Europ Resp J 1992; 5: 1068—1074.

Marano G, Fischioni P, Graziano C, Iannone M, Morisi G: Increased serum selenium levels in patients under corticosteroid treatment. Pharmacol Toxicol 1990; 67 (2): 120—122.

McKenzie RC, Rafferty TS, Beckett GJ: Selenium: an essential element for immune function. Immunology Today 1998; 19 (8): 342—345.

Misso NL, Powers KA, Gillon RL, Stewart GA, Thompson PJ: Reduced platelet glutathione peroxidase activity and serum selenium concentration in atopic asthmatic patients. Clin Exp Allergy 1996; 26 (7): 838—847.

Pearson DJ, Suarez-Mendez VJ, Day JP, Miller PF: Selenium status in relation to reduced glutathione peroxidase activity in aspirin-sensitive asthma. Clin Exp Allergy 1991; 21 (2): 203—208.

Shaw R, Woodman K, Crane J, Moyes C, Kennedy J, Pearce N: Risk factor for asthma symptoms in Kawerau children. N Z Med J 1994; 107: 387—391.

Stone J, Hinks LJ, Beasley R, Holgate ST, Clayton BA: Reduced selenium status of patients with asthma. Clin Sci 1989; 77 (5): 495—500.

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