Skeletal muscle magnesium and potassium in asthmatics treated with oral beta$_2$-agonists


ABSTRACT: Dietary magnesium has been shown to be important for lung function and bronchial reactivity. Interest in electrolytes in asthma has so far mainly been focused upon serum potassium, especially linked to beta$_2$-agonist treatment. It is known that serum levels of magnesium and potassium may not correctly reflect the intracellular status. We therefore investigated whether asthmatics treated with oral beta$_2$-agonists had low magnesium or potassium in skeletal muscle and serum, and whether withdrawal of the oral beta$_2$-agonists would improve the electrolyte levels. Magnesium and potassium levels in skeletal muscle biopsies, serum and urine were analysed in 20 asthmatics before and 2 months after withdrawal of long-term oral beta$_2$-agonists, and for comparison in 10 healthy subjects.

Skeletal muscle magnesium in the asthmatics was lower both before (3.62±0.69 mmol·100 g$^{-1}$ (mean±SD)) and after (3.43±0.60 mmol·100 g$^{-1}$) withdrawal of oral beta$_2$-agonists compared with the controls (4.43±0.74 mmol·100 g$^{-1}$). Skeletal muscle potassium and serum magnesium did not differ between the groups. Serum potassium was significantly lower both before (4.0±0.2 mmol·L$^{-1}$) and after (3.9±0.2 mmol·L$^{-1}$) the withdrawal of oral beta$_2$-agonists compared with the control group (4.2±0.2 mmol·L$^{-1}$).

The asthmatics had lower skeletal muscle magnesium and lower serum potassium than the healthy controls, both with and without oral beta$_2$-agonists. Whether the findings are related to asthma pathophysiology or treatment is currently being investigated.


Bronchial asthma is a common disease for which the underlying mechanisms are not fully known. The importance of dietary magnesium for bronchial tonus and airway reactivity has recently been highlighted by Britton et al. [1]. Magnesium sulphate is known to cause bronchodilatation in treatment of asthma attacks [2–4]. Magnesium is also essential for normal potassium levels, being a co-factor for sodium-potassium-adenosine triphosphatase (ATPase) in the cell membrane [5]. It is well-known that beta$_2$-agonist treatment can reduce serum potassium [6, 7], which has been feared to contribute to arrhythmias in fatal asthma [8, 9]. The hypokalaemia can be further enhanced by concomitant theophylline treatment [10] and by diuretics [11].

So far, the concern about electrolytes in asthma has been focused on measurements of serum levels. However, it is known that most of the total body potassium and magnesium is intracellular and that deficiency of these ions can exist despite normal contents in serum [12, 13]. Until now, there have been, to the best of our knowledge, no reports on tissue electrolytes in asthmatics. We postulated that oral beta$_2$-agonist treatment in these patients could alter not only serum electrolytes but also tissue electrolytes. Since only diminutive amounts of bronchial tissue may be obtained from asthmatics in vivo, we chose to use skeletal muscle tissue as a model to sample sufficient amounts of human muscle tissue in vivo to assay muscle electrolytes.

The aim of the present study was to investigate whether asthmatics on treatment with oral beta$_2$-agonists had lower potassium and magnesium in skeletal muscle and serum compared with healthy subjects. We also wanted to determine whether cessation of the oral beta$_2$-agonists, in that case, would improve the electrolyte levels in these asthmatics.

Subjects

Twenty two out-patients with regular controls at the Department of Internal Medicine, Skellefteå County Hospital, who had bronchial asthma diagnosed according to the definition of the American Thoracic Society [14] entered the study. The diagnosis was based upon...
clinical history, forced expiratory volume in one second (FEV1) reversibility of more than 15%, diurnal variability more than 20% of peak expiratory flow rate (PEFR) or positive methacholine test. Two patients failed to complete and were not evaluated further (denial of further participation and loss of one muscle sample, respectively). Thus, 20 patients completed the study (11 males and 9 females, aged 50±11 yrs (mean±SD). Their mean duration of asthma was 18.2±11.4 yrs (mean±SD), and their mean FEV1 at the time of the study was 86±23% of predicted (mean±SD). Twelve patients were nonsmokers and eight were ex-smokers. All patients were treated with inhaled steroids (daily dose 1,245±490 µg, mean±SD) and inhaled short-acting β2-agonists. All patients also had β2-agonist tablets with prolonged action; terbutaline in 19 patients and salbutamol in 1. One patient had 7.5 mg once daily, and the other 19 patients 5–8 mg twice daily. All patients were clinically stable and there were no obstacles for withdrawal of the oral β2-agonists. Four patients had nebulizing therapy with β2-agonist and nine patients had theophylline tablets. Exclusion criteria were treatment with oral steroids, diuretics or potassium sparing agents.

Ten healthy subjects, mainly hospital staff, asymptomatic and with normal lung function (FEV1 114±12% pred) served as a control group (5 males and 5 females, aged 48±9 yrs). Two control subjects were smokers.

Methods

Following a prestudy visit the patients returned for Visit 1, when skeletal muscle biopsy, blood and 24 h urine samples were collected and FEV1 and vital capacity (VC) were measured. Oral β2-agonists were then withdrawn, whilst the other asthma medications were unchanged. After 2 months, the same investigations were performed at Visit 2. PEFR and the use of inhaled β2-agonists were recorded during 1 week before and after Visit 1 and during the week before Visit 2. A short course of oral steroids was allowed during the study if deterioration occurred. In the healthy control subjects, skeletal muscle biopsies, blood and 24 h urine samples were taken on a single occasion.

Muscle biopsies were performed by a percutaneous needle technique developed by Bergström [15]. All specimens were taken from the lateral portion of the quadriceps femoris muscle, 15–20 cm proximal to the knee. The muscle tissue (in our study weighing 4.1–41.4 mg, mean 14.9 mg) was placed on a piece of quartz glass and with nonmetal tweezers carefully dissected free from all visible fat and connective tissue. All traces of blood were wiped off by rolling the specimens on the piece of quartz glass. The muscle tissue was then placed on a platinum hook and dried in an oven at 110°C to constant weight, extracted in 1 mL of petroleum ether for 2 h and dried to constant weight again, and the fat-free dry solids (FFDS) weight was calculated. The electrolytes were extracted from the muscle tissue by treatment with 250 µL 2.5 M HNO3 for 24 h. From each sample, 100 µL of the supernatant was diluted to 10 mL with 0.25% SrCl2 and analysis for Mg and K in the tissue was performed on an Atomic Absorption Spectrophotometer (Varian 1275). The results were calculated in mmol·100 g−1 FFDS. For a proper quality control of the measurements, a certified reference material was used (IAEA animal muscle (H-2) from International Atomic Energy Agency, Vienna, Austria).

Serum and urine concentrations of potassium were analysed by conventional autoanalyser technique and of magnesium by atomic absorption. Reference values were the following: serum potassium 3.6–4.5 mmol·L−1; serum magnesium 0.7–1.0 mmol·L−1; urine potassium 50–100 mmol·24 h−1; and urine magnesium 2.5–7.5 mmol·24 h−1.

The study was blinded for the technicians who analysed the serum and skeletal muscle samples. The study was approved by the Local Committee of Ethics. The participants were informed in writing and their consent was obtained orally.

Statistics

Student’s t-test for paired observations (Statview®, Abacus Concepts for Macintosh®) was used for comparison of the serum, muscle and urine values in the asthmatics and for comparison of FEV1 at the beginning and at the end of the study. Unpaired t-test was used for analysis of the differences in electrolyte concentrations between the asthmatics and the healthy subjects. Wilcoxon signed rank test was used for comparison of consumption of β-agonists as needed at the beginning and at the end of the study. Calculations were made with 95 percent confidence intervals (95% CI) and a p-value of 0.05 or less was regarded as statistically significant.

Results

Two patients deteriorated and required a short course of oral steroids, during week three and seven, respectively, after withdrawal of oral β2-agonists. The other patients were clinically stable throughout the study. FEV1 before and after the withdrawal of oral β2-agonists was (mean±SD) 78±28% and 81±25% pred, respectively, a difference which was not statistically significant. The dosages per day of inhaled aerosol or powder of β2-agonist were significantly fewer (p<0.05) during the week before withdrawal of oral β2-agonists (median 5.4; 5th–95th percentiles 0.0–14.4) compared with the last week of the study (median 6.3; 5th–95th percentiles 0.0–16.9). The usage of nebulized salbutamol/terbutaline was unchanged between these two weeks for the four patients who had nebulizers at home. Due to missing data, urine magnesium was analysed in 19 samples before stopping oral β2-agonists, in 20 after stopping, and in 8 healthy subjects. For urine potassium the numbers were 14, 20 and 9, respectively.

Skeletal muscle magnesium (table 1) was significantly lower in the asthmatics, both before and after the termination of oral β2-agonists, compared with the control
Interest in magnesium levels in asthma dates back to the first half of this century, when low serum magnesium levels were shown in some asthmatics, who were successfully treated with magnesium sulphate [20]. Magnesium acts as a calcium antagonist and affects smooth muscle tone [20, 21]. In recent years, there has been evidence that hypomagnesaemia can contribute to increased bronchial reactivity [1, 22], which in turn can be reduced by inhaled magnesium sulphate [23, 24]. Several studies have shown a bronchodilating effect by intravenous magnesium sulphate in asthma deterioration [2–4] and it has been proposed as an adjunctive treatment in patients with poor response to β2-agonists. In a study on the bronchodilating effect of intravenous magnesium sulphate in six patients with acute severe asthma [4], both serum levels and intracellular concentrations (erythrocytes) of magnesium were within normal limits. An investigation in chronic obstructive pulmonary disease (COPD) patients admitted to the Intensive Care Unit [25] showed low muscle magnesium values in 15 (47%) of 32 patients but no alteration of serum magnesium levels. Serum magnesium falls in response to high catecholamine levels, for example in acute myocardial infarction, and it has also been shown to fall in patients receiving infused but not inhaled β2-agonists [19].

In contrast to the differences described in the level of skeletal muscle magnesium, the potassium level in skeletal muscle was not different in asthmatics compared with controls, which contrasts with the findings of Piaccardori et al. [25], who found lower muscle and intracellular potassium in patients with COPD admitted to the Intensive Care Unit.

Potassium in serum, on the other hand, was significantly lower in the asthmatics compared with the control group, and it fell significantly after withdrawal of oral β2-agonists. The reason for these findings is unclear. Previous studies have not demonstrated prolonged depression of serum potassium by β2-agonists [26, 27].

Skeletal muscle potassium in the asthmatics and in the control group was slightly lower compared with earlier studies on healthy subjects. Widman [28] and Sjögren [29] reported mean values of 43.70 and 46.40 mmol·100 g⁻¹ FFDS, respectively. This may be due to differences in the atomic absorption method used. However, it does

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**Table 1.** Magnesium and potassium in skeletal muscle, serum and urine of asthmatics (n=10) before and 2 months after termination of oral β2-agonists compared with healthy subjects (n=10)

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Asthmatics Before</th>
<th>Asthmatics After</th>
<th>Healthy subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle-Mg</td>
<td>3.62±0.69**</td>
<td>3.43±0.60***</td>
<td>4.43±0.74**,***</td>
</tr>
<tr>
<td>Muscle-K</td>
<td>37.8±5.06</td>
<td>36.1±4.17</td>
<td>34.1±5.87</td>
</tr>
<tr>
<td>Serum-Mg</td>
<td>0.93±0.10</td>
<td>0.92±0.09</td>
<td>0.89±0.06</td>
</tr>
<tr>
<td>Serum-K</td>
<td>4.0±0.21±0.0</td>
<td>3.9±0.20***</td>
<td>4.2±0.21***</td>
</tr>
<tr>
<td>Urine-Mg</td>
<td>5.2±2.4</td>
<td>5.7±2.7</td>
<td>6.5±3.5</td>
</tr>
<tr>
<td>Urine-K</td>
<td>71±23</td>
<td>65±22</td>
<td>64±38</td>
</tr>
</tbody>
</table>

Values are presented as mean±sd. Asthmatics vs healthy subjects: *: p<0.05; **: p<0.01; ***: p<0.001. Asthmatics before vs after termination or oral β2-agonists. °°: p<0.01. FFDS: fat-free dry solids.
not affect the outcome of the results in this study, since we included a parallel healthy control group for comparison.

In conclusion, we found low tissue magnesium in asthmatics compared with the healthy subjects. Whether this is related to the pathophysiology of asthma or a pharmacological effect is currently under investigation.

References